17/11/2008

KIBM lecture 1/6 — Heterocycles

KIBM: N306

Think about this course as "Heterocyclic Chemistry : Part 1" – as Part 2 is KIBM's course next year.

- Heterocycles are essential components of drugs
- But the field is enormous
- KIBM will focus on the basics and single cases.

Heterocyclic compounds

Two classes

(a) Aromatic

– 5-membered

pyrrole — smells like other amines

furan — smells like fruity pond

thiophene — smells like freshly cut grass – quite nice

Similar but smell different, have different bp's.

– 6-membered

pyridine

(b) Saturated

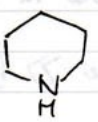
– 5-membered

pyrrolidine

tetrahydrofuran (THF)

tetrahydrothiophene

– 6-membered



piperidine

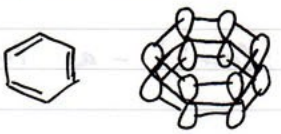
– 3-membered

epoxides:

oxirane (ethylene oxide)

Heteroaromaticity

Recall benzene

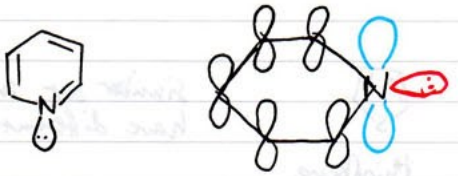


6 π electrons in a delocalised cyclic π-cloud

Hückel's Rule

$4n+2$ = no. of conjugated cyclic π electrons.
where n is an integer

Pyridine

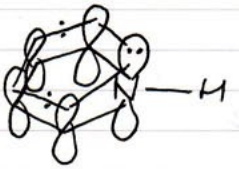


lone pair is at 90° to 6 π-cloud ∴ not involved in aromaticity

lone pair is basic and nucleophilic.

5-Membered Heteroaromaticity

each double bond is two electrons.



6 π electrons delocalised over 5 atoms.

6π (2 × 2π + lone pair) = aromatic

pyrrole is non-basic and non-nucleophilic.

All three (N, S, O) are more electron rich than benzene. – sometimes called "π-excessive" heterocycles.

Much more reactive than benzene in aromatic substitution.

Pyrrole > Furan > Thiophene >> Benzene

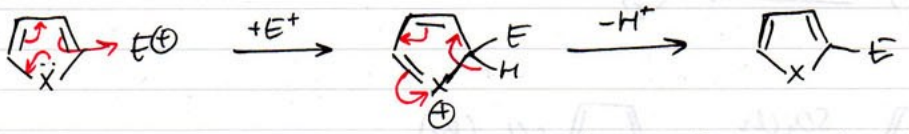
10^7 10^2 1 $\sim 10^{-2}$

clear liquid when distilled but after half an hour or so it goes smoky brown as it reacts with atmospheric CO_2 and it reacts with itself under acid catalysis.

Electrophilic substitution

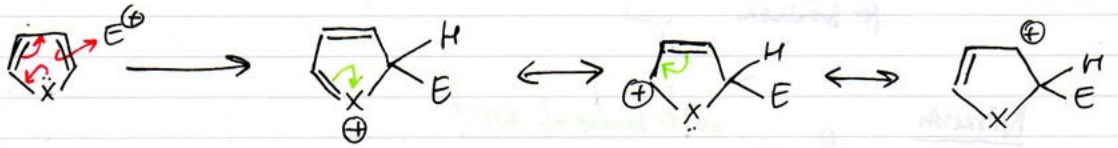
Ring reacts at the 2 position in the first instance.

(Stoichiometric quantities of reactants gives 2-sub'ed cleanly. Excess electrophile gives polysubstitution).



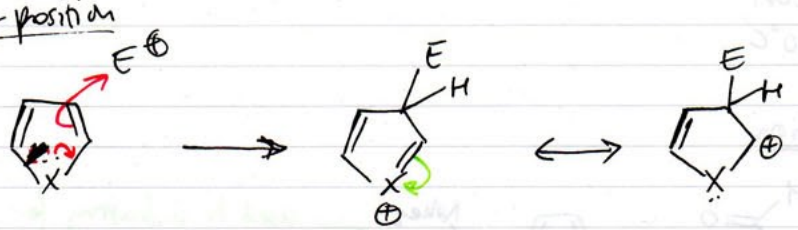
Thermodynamically driven – intermediate not aromatic, product is.

2 position

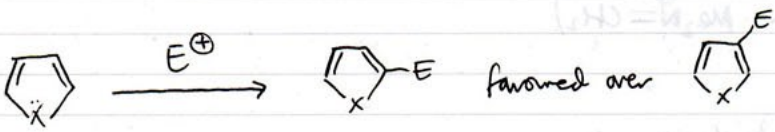


3 resonance stabilised forms.

3-position



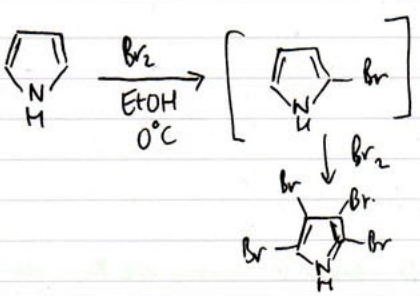
only 2 resonance stabilised forms.



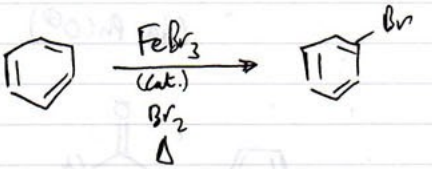
favoured over

(use resonance to predict)

much more reactive than benzene
∵ electron rich ∴ do not generally need a catalyst for EAS.
but often difficult to stop them overreacting.

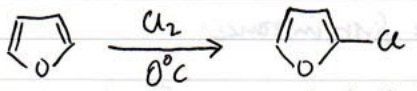


cf.



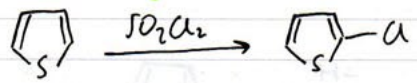
So do it at −78°C
and v. carefully add just 1 eq. Br

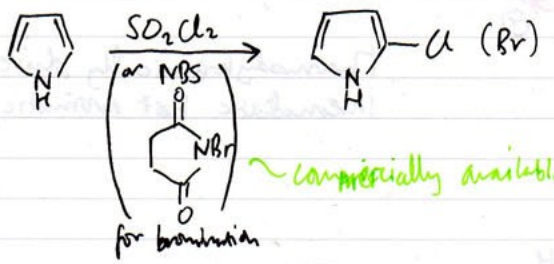
Halogenation



v. high yield

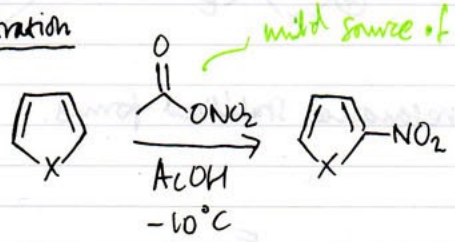
milder, more controlled chlorinating agent than Cl_2



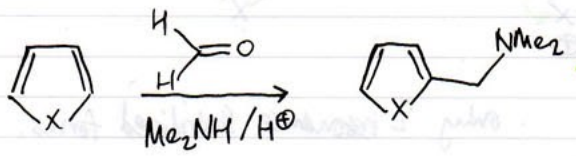


~ commercially available mild source of bromine

Nitration



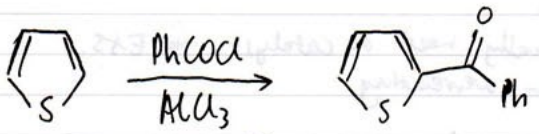
Mannich Reaction



used in industry for further functionalisation.

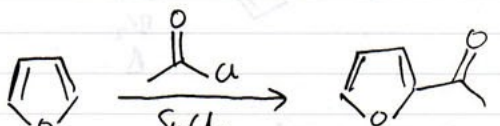
(via $Me_2\overset{\oplus}{N}{=}CH_2$)

Friedel-Crafts Acylation

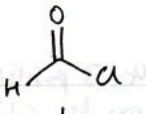
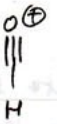


(via $PhCO^\oplus$)

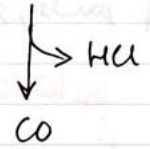
also works for any R group in place of Ph.



(can use milder cat. than $AlCl_3$ - also useful ∵ liquid - easier to handle and than reactive solid $AlCl_3$

NO Friedel-Crafts equivalent for  

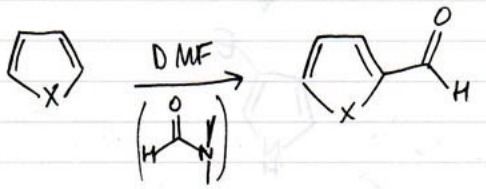
Forms chloride is not stable – decomposes to CO + HCl.



Vilsmeir Reaction

CORRECT SPELLING IS VILSMEIER

Related to the Mannich rxn. Works with all 3 heterocycles. Don't get overreaction.

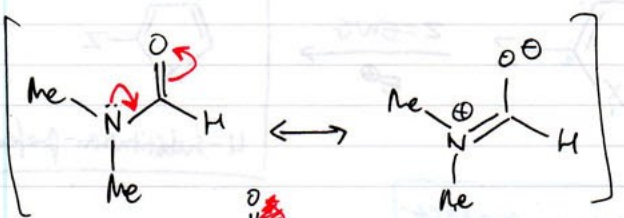


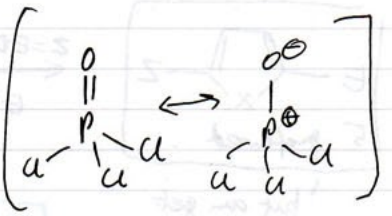
$POCl_3$ then H_2O

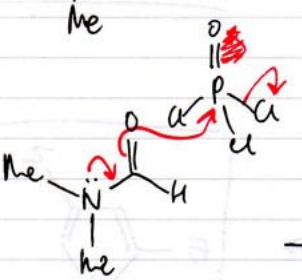
this reaction is not an option for benzene – really down to the superior reactivity of these heterocycles.

TWO MAIN STEPS: ① GENERATION OF VILSMEIR INT. BY DEHYDRATION OF DMF

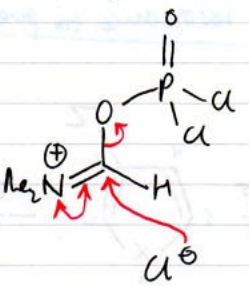
②

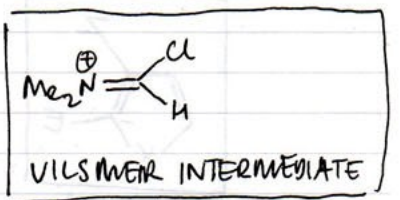






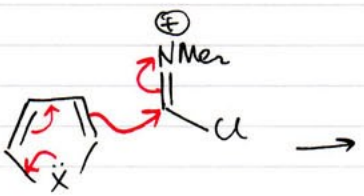
phosphorus has v. high affinity for oxygen – strong P–O bond formed.

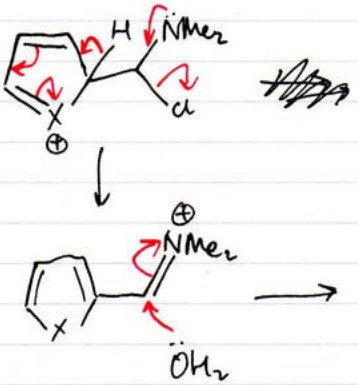


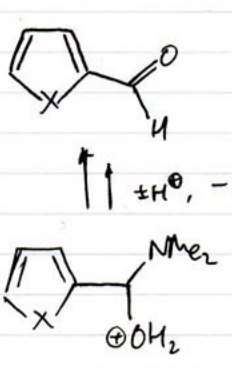


VILSMEIER INTERMEDIATE

v. reactive chloroiminium ion (orders of magnitude more reactive than $Me_2N^{\oplus}=CH_2$)



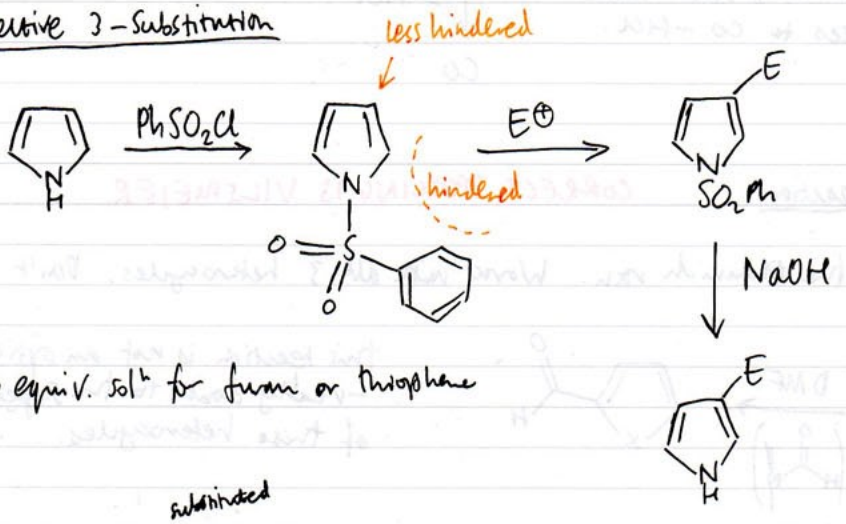




$\pm H^{\oplus}$, $-NHMe_2$, $-H^{\oplus}$

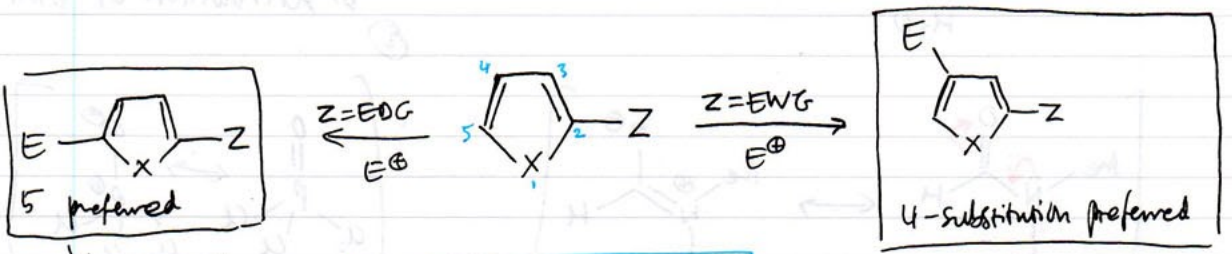
⚠ How to substitute selectively at 3 position? Unsolved industrial problem - if you want to make millions of pounds, solve it! Look at price difference between 2 and 3 subst'd heterocycles.

Selective 3-Substitution



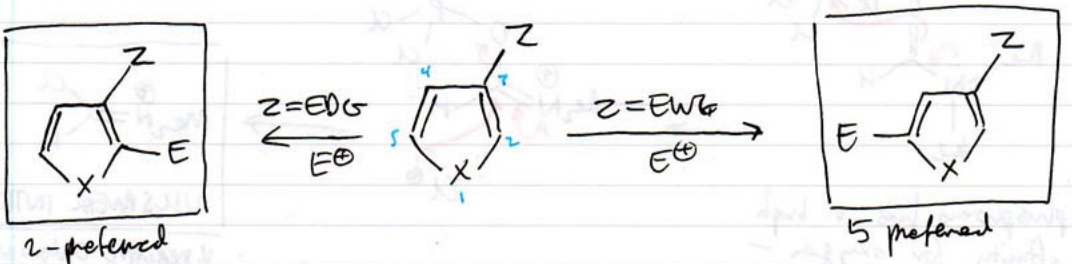
no equiv. sol'n for furan or thiophene

Substitution of substituted heteroaromatics



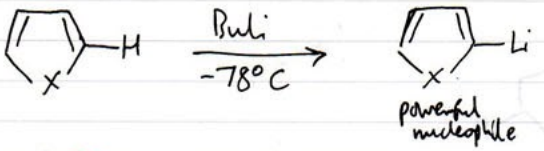
but can get mixtures.

use resonance to predict

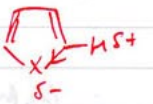


(b) Metallation

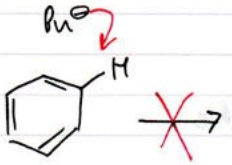
Works for all the heterocycles.



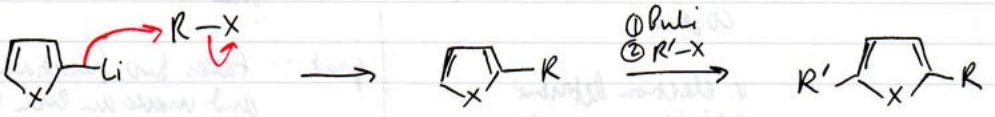
Works for heterocycles due to the inductive effect - leaves H acidic



X more electronegative than C



benzene protons not acidic enough.



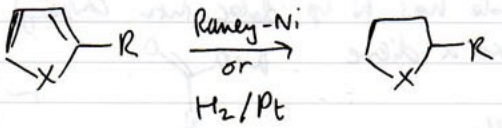
carefully add BuLi to prevent heterocycle, deprotonate & lithiate, then react with an electrophile. Quick and easy route to highly substituted heterocycles.

X = O, S, NR

X ≠ NH (too acidic).

(c) Reduction

THF made by reduction of furan.

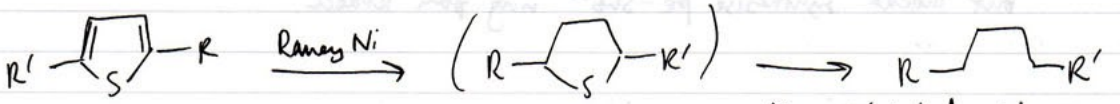


cf. benzene which is harder to reduce, needs high T, p.

tetrahydro Systems.

Raney Nickel - spongy metal, massive SA, absorbs lots of H_2. - white knuckle ride
- Sparks and glows red hot, sets fire to solvent since it has adsorbed loads of O_2 when solvent removed.
- KiBh set fire to a bin when a young PhD student using RaNi.

Thiophenes

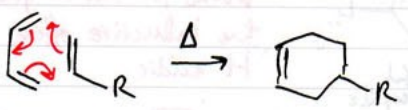


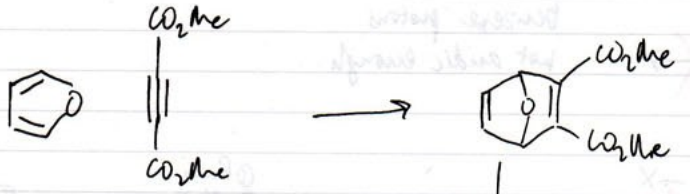
Thiophene has same T_b as octanes in petrol
∴ v. hard to distill off from crude oil ∴ need to desulfurize
∴ use RaNi catalyst!

very useful industrial route to long chain hydrocarbons
- good way to put a C_4 spacer in

d) Cycloaddition – generally only works really well for furan

Diels-Alder (4+2)

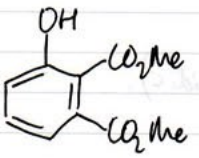




v. electron deficient acetylene – good dienophile

good ∵ takes two functionalised cmpds and makes an even more funct. one

$H^{\oplus}$



fast WS Q not easy – think of formula rxn as Diels Alder

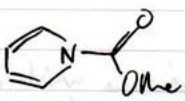
work out mechanism in workshop – then write it up here:

not easy (impossible with short route) using EAS.

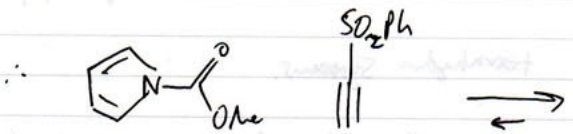
∴ this is a very useful complementary synthesis

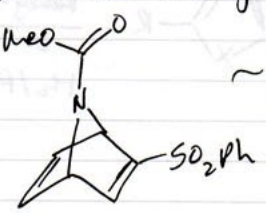
pyrrole and thiophene are much harder – do not want to give up their aromaticity

benzene never does DA, pyrrole/thiophene hard, furan easier.



this pyrrole has N lp deloc. into carbonyl ∴ behaves more like a diene





– these ring systems common in eg. cocaine, pharma, poison tree frog toxin, epibatidine – spray was addictive morphine

(reversible) – retro-DA gives aromatic cmpd ∴ to push to RHS need to make reactant less aromatic

V. good rxn but tricky to do – need pressure

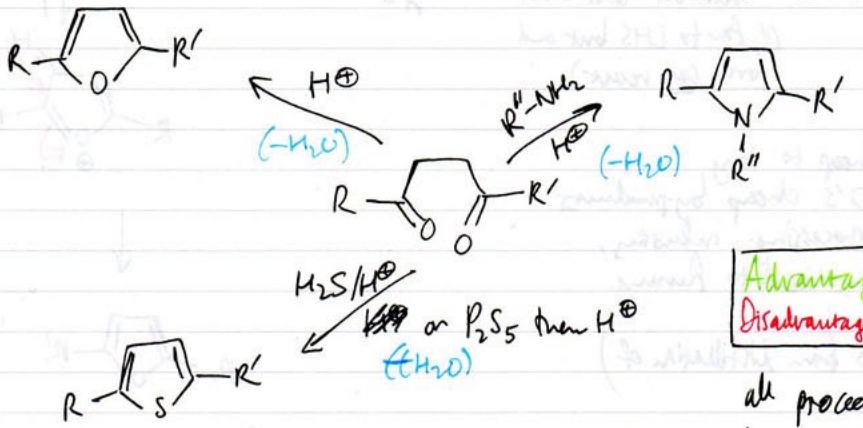
if TM has more than one substituent, better not to functionalise the parent ring, but instead synthesise pre-subst ring from scratch.

Synthesis of Heterocycles

General route: Paal-Knorr Synthesis. (Paal (Swedish), Knorr (German)) — v. prolific

Starting material: 1,4-diCO

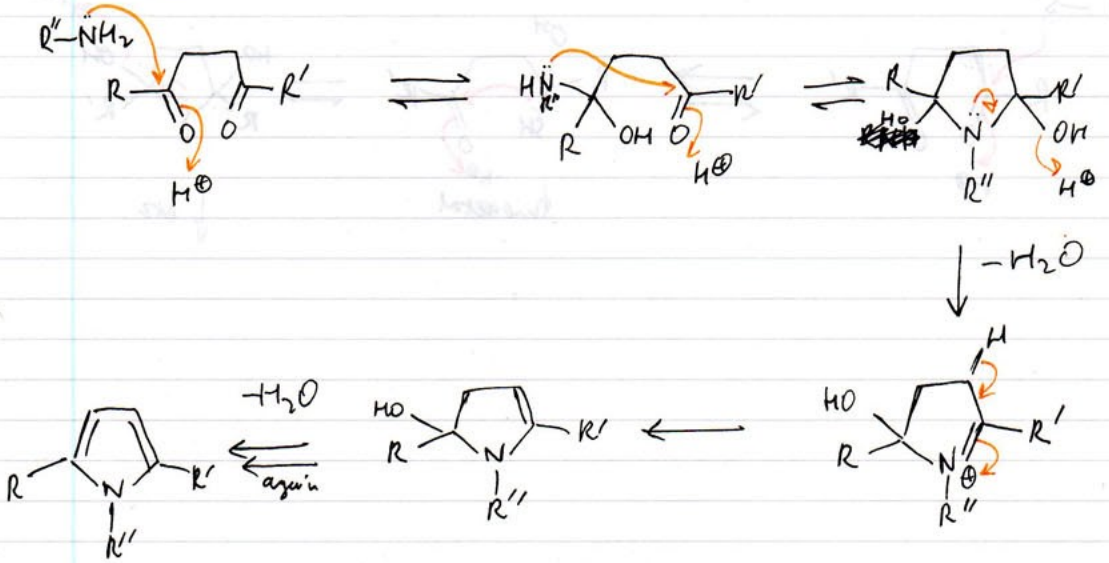
H_2S v. toxic (SO_x toxicity of HCN) ∴ need to avoid industrially.



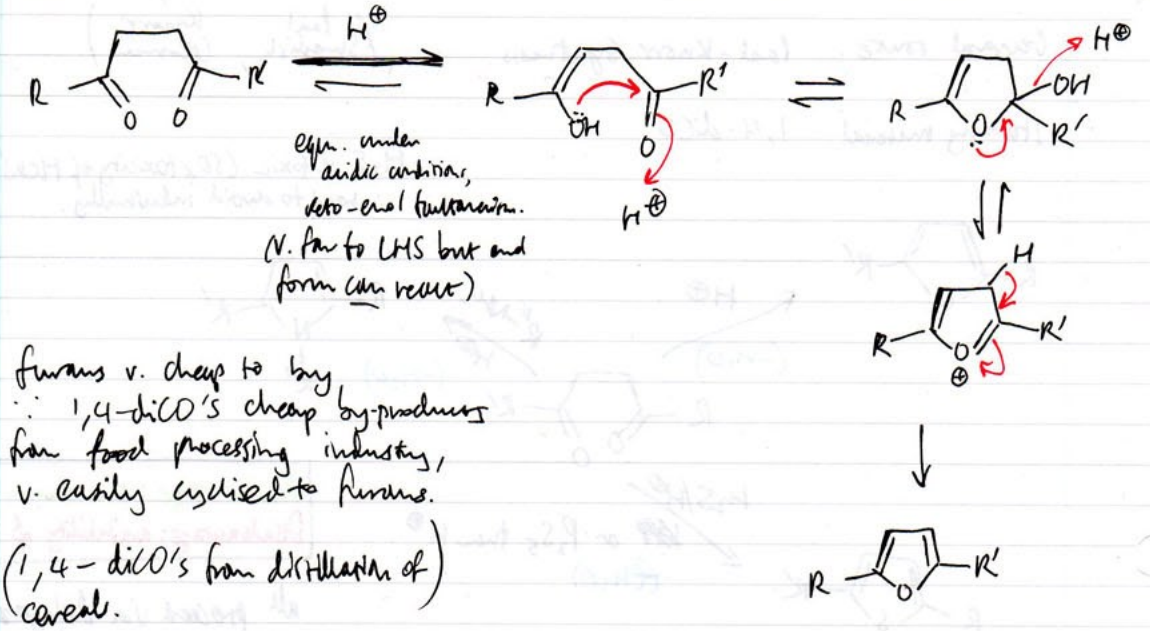
Advantage: one common starting material
Disadvantage: availability of 1,4-dicarbonyls

all proceed via dehydration. mechanism not that difficult.

pyrrole

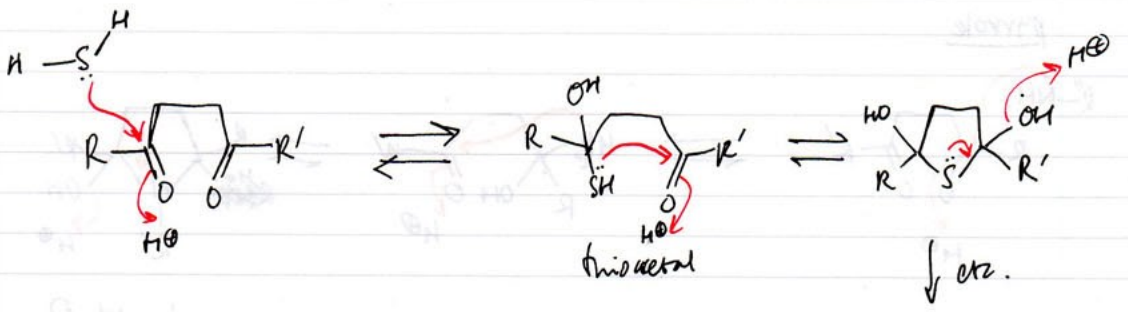


Furan



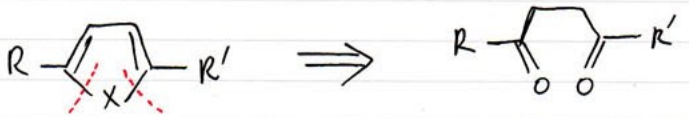
furans v. cheap to buy
∴ 1,4-diCO's cheap by-products from food processing industry, v. easily cyclised to furans.

(1,4-diCO's from distillation of cereal.



Summary:

P–K retrosynthesis

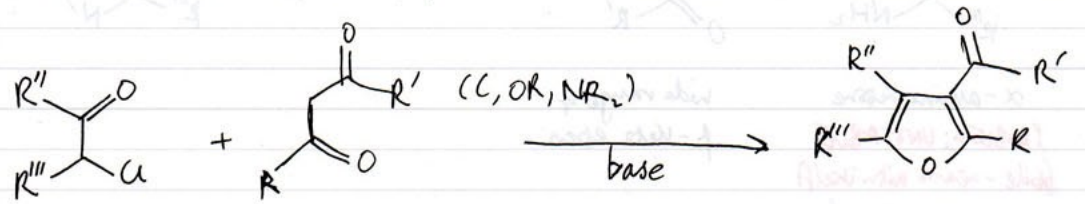


but must be able to get your hands on the required 1,4-diCO

Furans

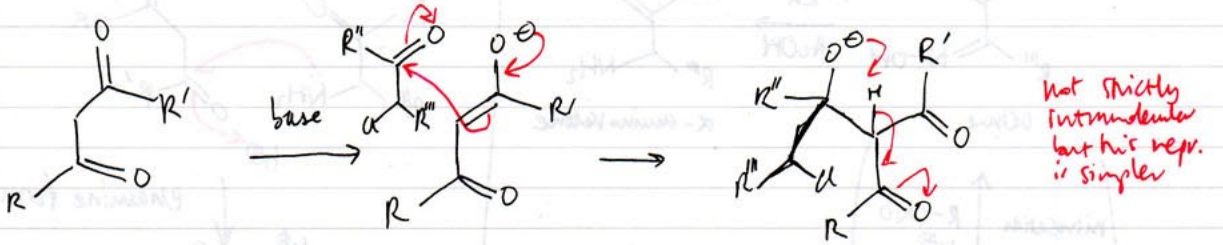
Feist - Benary Synthesis

v. flexible, method of choice for the synthesis of furans.



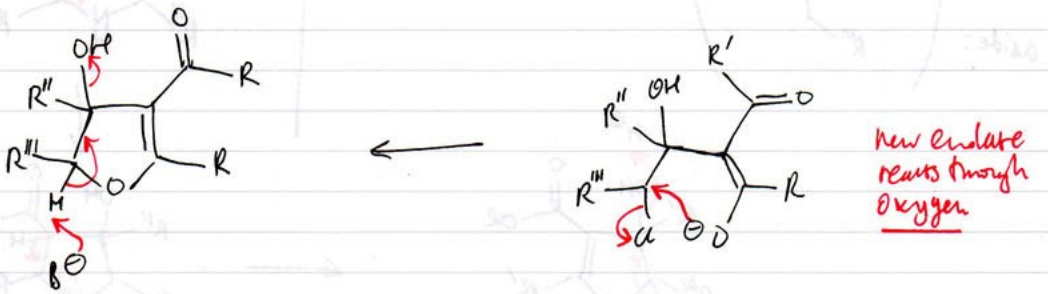
α-chloroketone (readily available from the ketone)

β-keto ester (α-proton more acidic than that of α-chloroketone)



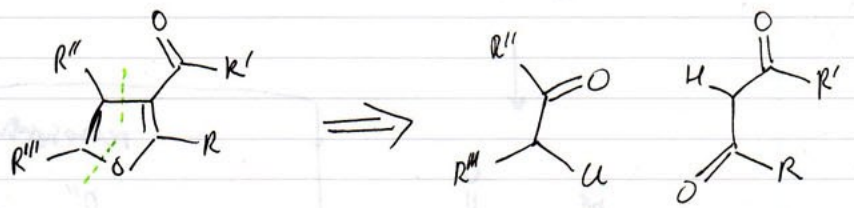
not strictly intermediates but this repr. is simpler

proton transfer

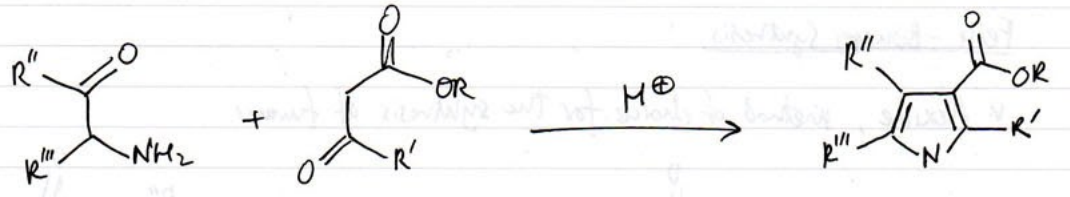


new enolate reacts through Oxygen

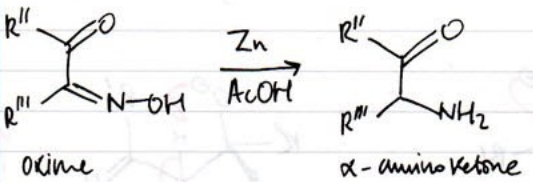
Retrosynthesis



Pyrroles: Knorr synthesis



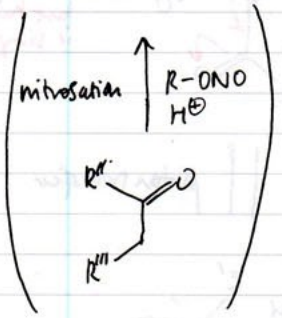
α-amino ketone
PROBLEM: UNSTABLE
(base - reacts with itself)
so make in situ from corresponding oxime by reduction:

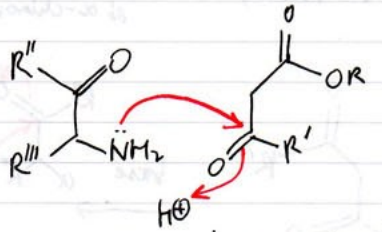


oxime

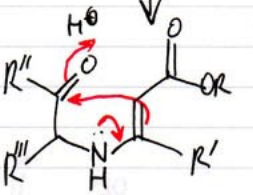
α-amino ketone

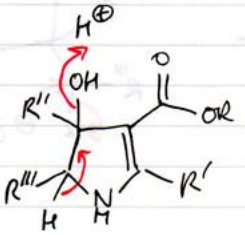
aside:

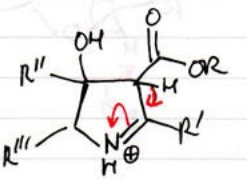


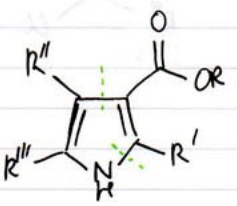


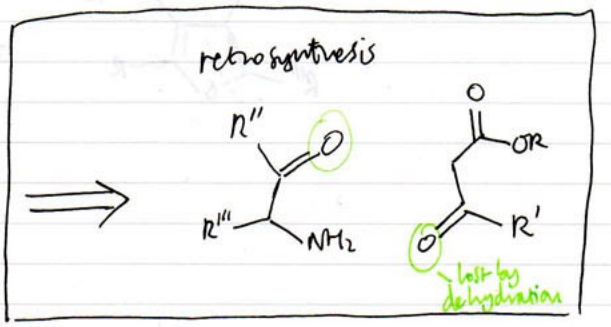
enamine formation





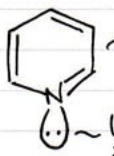






there are no general thiophene synthesis; no thiophene equivalent of Knorr or Feist-Benary syntheses ∴ stick to Paal-Knorr for [1,5]

Pyridine and its derivatives

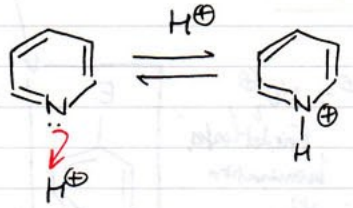


ring is v. stable and unreactive
soluble in water and organic solvents

lone pair not involved in aromaticity ∴ basic or nucleophilic (at 90° to 6π aromatic system) available for bonding

unpleasant odour (ouzo/Pernod smell)

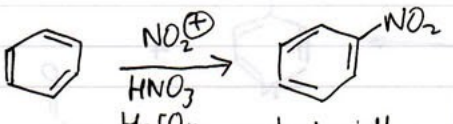
exposure to too much will make men sterile



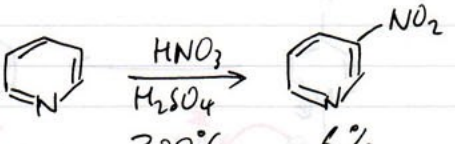
pKa 5.2
quite acidic ∴ pyridinium is a useful weak acid.

Weaker base than Et_3N ∴ if Et_3N is giving trouble (side-products or), consider py.

Reaction with electrophiles



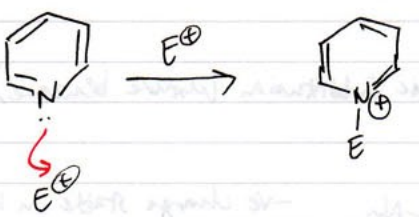
high yield (90 odd %)



6 %

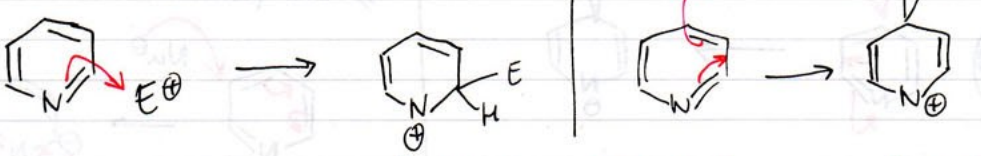
NOT USEFUL CHEMISTRY

Three problems with pyridine

① 

generates an inert salts - kills off rxn

② Due to electronegativity of nitrogen, pyridine ring is electron deficient (compared to benzene). "π-deficient".

③ 

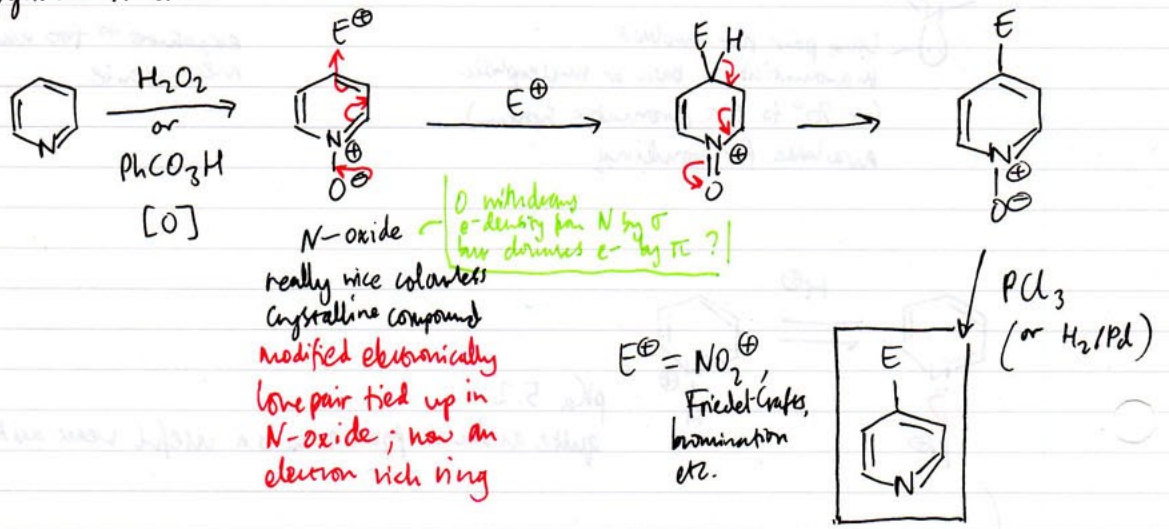
2 or 4 posn V. bad news for EAS

(positive charge on N w/ only two bonds (divalent) - v. high energy, unstable } missing a bond AND has a +ve charge

Need indirect methods for substituting the pyridine ring.

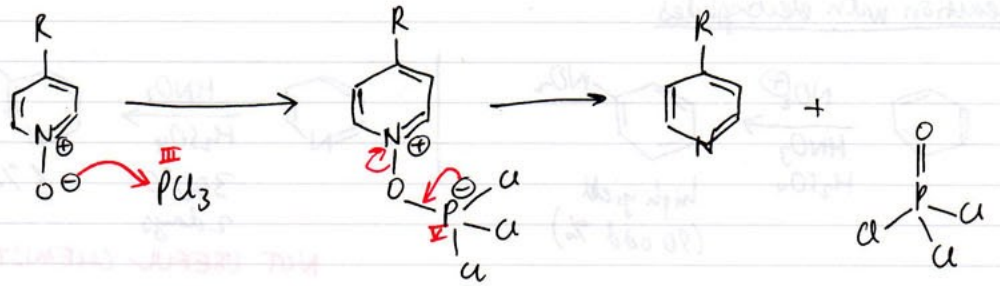
Indirect Substr. Methods

pyridine N-oxide



SO YOU CAN DO EAS ON PYRIDINE BUT NEED TO DEAL WITH LP FIRST.

Mechanism of N-oxide reduction with PCl_3:



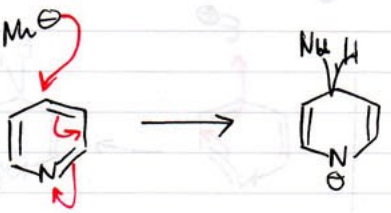
Nucleophilic Substitution

Pyridine's main reactions are nucleophilic substitution (unlike benzene).

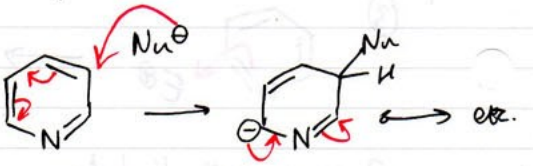
2/

-ve charge stable on N.

4/ (eg. if 2 positions blocked)

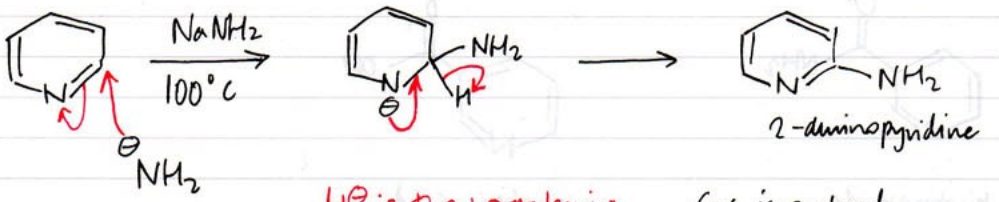


3/ not favourable



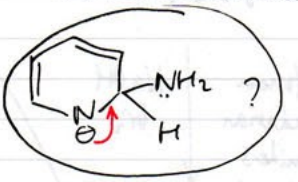
all you do is destroy aromaticity, without putting a -ve charge on N.

Chichibabin Reaction

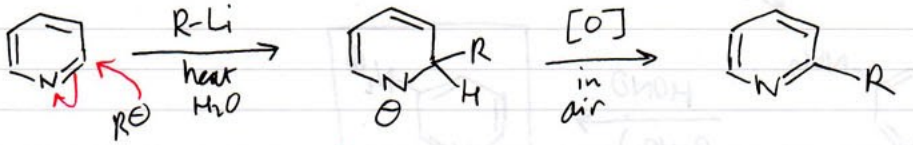


$H^{\ominus}$ is the worst leaving group possible — don't apply this logic anywhere else! KIBM thinks this rxn is thermodynamically wrong. But generally accepted.

Gas is evolved during the rxn
- 3 coordinate mechanism?

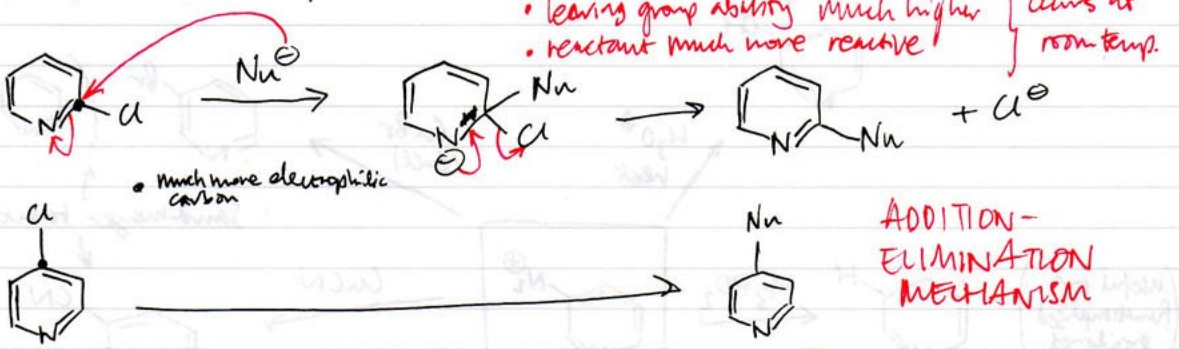


↑ H_2 ?



does not eliminate $H^{\ominus}$

Leaving group in 2/4 positions



- leaving group ability much higher
- reactant much more reactive

} occurs at room temp.

- much more electrophilic carbon

ADDITION-ELIMINATION MECHANISM

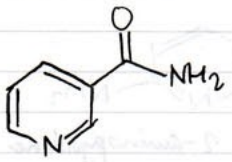
$Nu^{\ominus}$ = $MeO^{\ominus}$, $^{\ominus}OH$, $RS^{\ominus}$, NH_3, RNH_2, 

allows you to build in functionality not possible via Chichibabin or RLi methods.

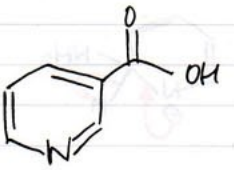
Why? Negative charge in intermediate never ends up on nitrogen, so there's no desire for the $Nu^{\ominus}$ to add in the first place. Same as for PhCl; no electron sink.

2/4 subst by cheap
3 subst by 10× more expensive

3 - Substitution



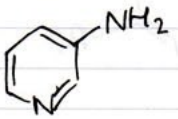
nicotinamide
(a natural product, very cheap indeed)

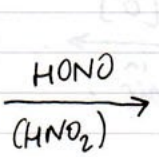


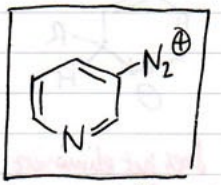
nicotinic acid
(again, naturally sourced, v. cheap)

Hoffman degradation of amides (2nd term) (GCLT)

NaOH
Br_2

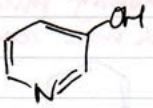


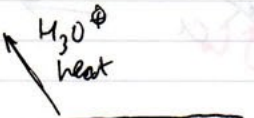


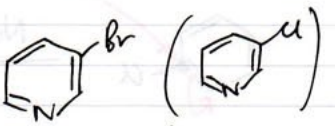


BUILDING BLOCK

v. useful, v. difficult to make by other methods

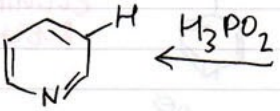


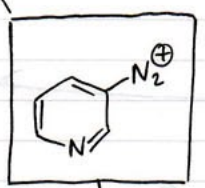


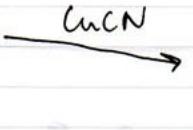


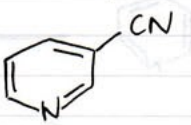
Sandmeyer reactions

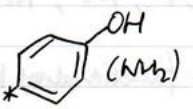
(useful for functionalised pyridines)

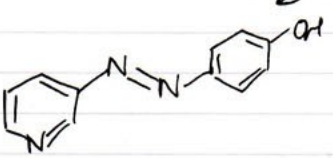








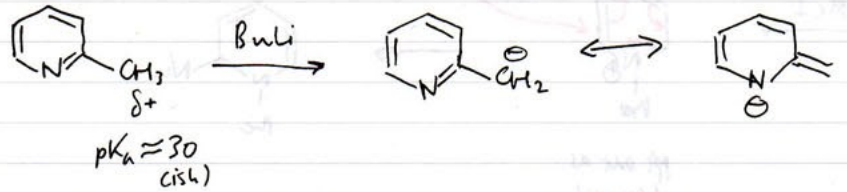


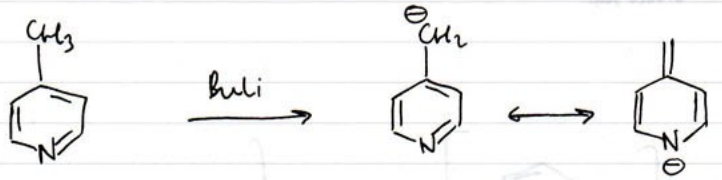


pyrido azo dyes incredibly important - water soluble etc.

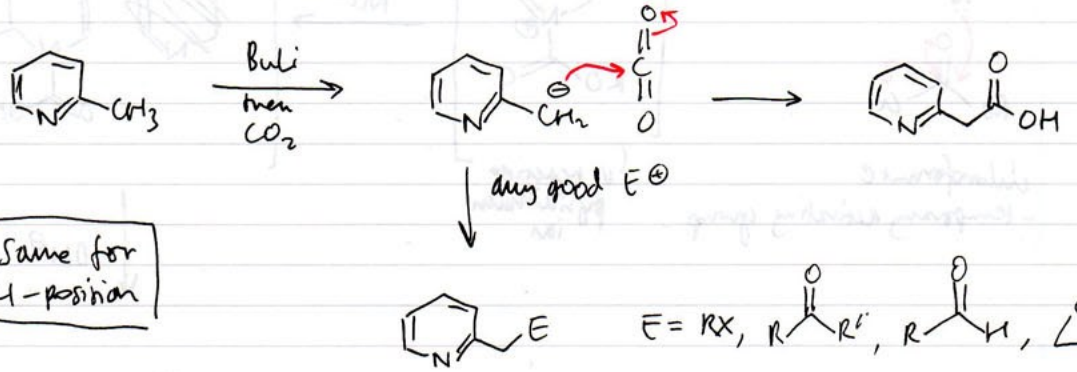
Alkyl pyridines

2-methyl pyridine (picoline) smells of butterscotch





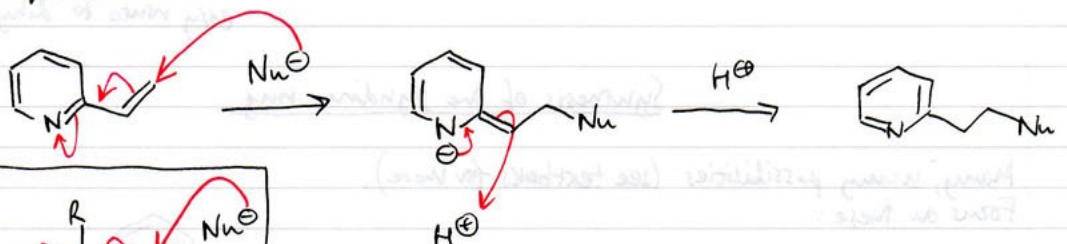
really good access to these reactive anions.



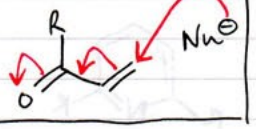
Same for 4-position

3-position is difficult (but not impossible).

Vinyl pyridines

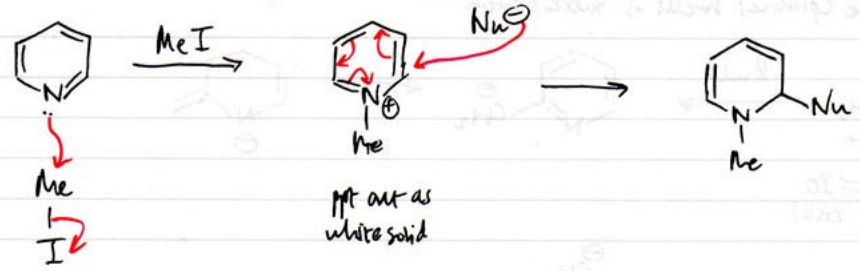


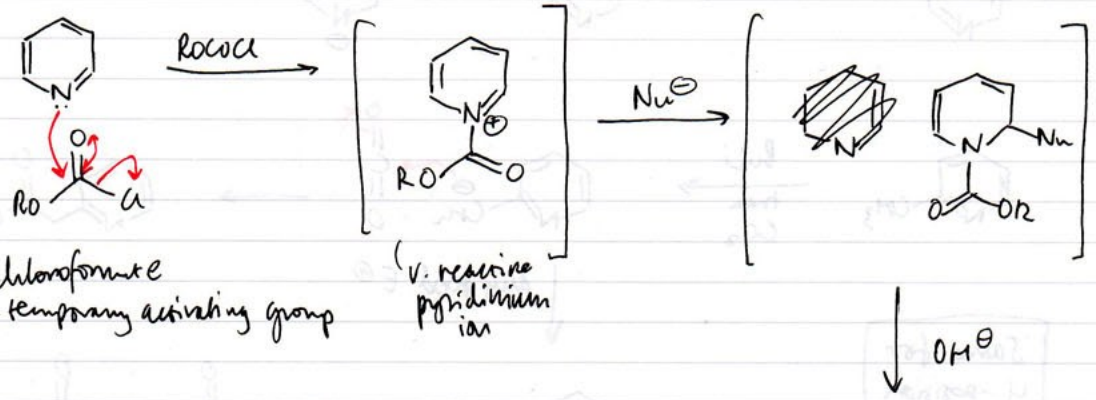
cf.



if TM is a pyridine with an ethyl spacer and then a group, try this Nu⊖ route.

Pyridinium salts

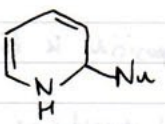




chloroformate
- temporary activating group

(v. reactive pyridinium ion)

$OH^{\ominus}$

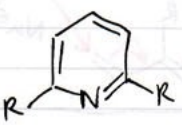


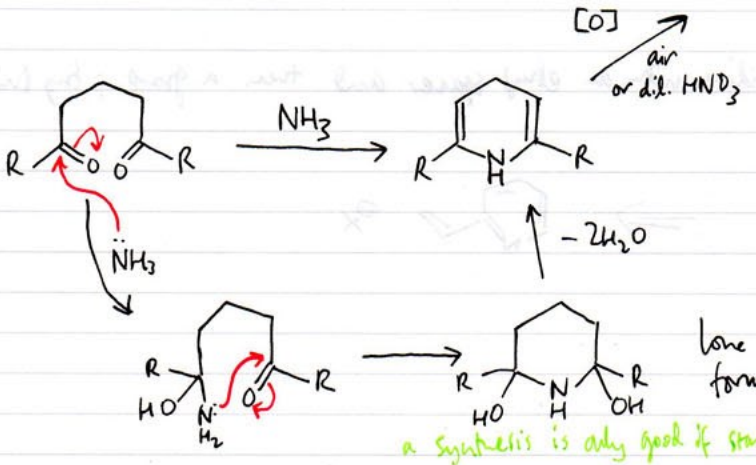
easy route to dihydro systems.

Synthesis of the pyridine ring

Many, many possibilities (see textbooks for more).
Focus on these:

(i) From 1,5-dicarbonyls (cf Paal-Knorr)



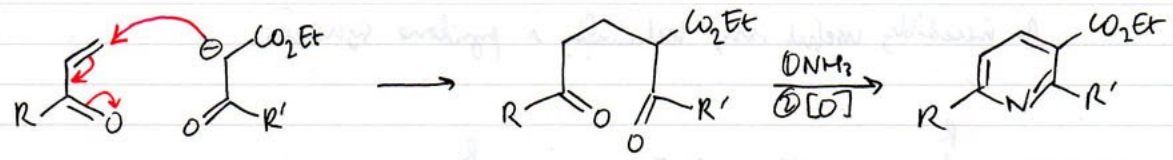


NADH is nature's hydride. Works on dihydropyridine, which is v. easily oxidised

lone pair on N expels H_2O, forms iminium then enamine

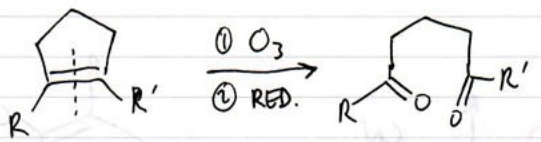
a synthesis is only good if starting materials available cheaply

Routes to 1,5-dicarbonyls:



1,4-addition
(conjugate ~~of~~ Michael)

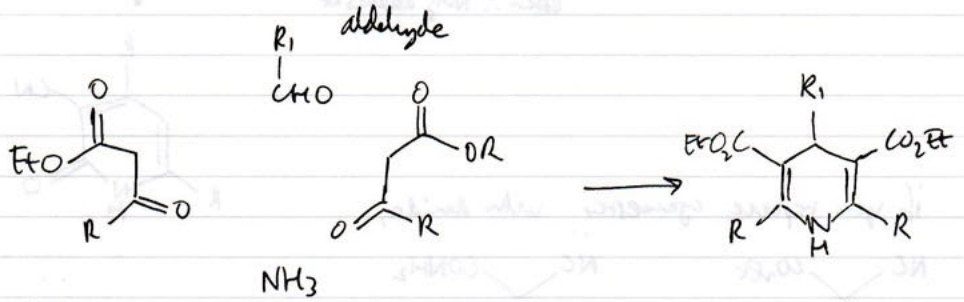
OR ozonolysis



good yield, works well.

(b) Hantzsch pyridine synthesis

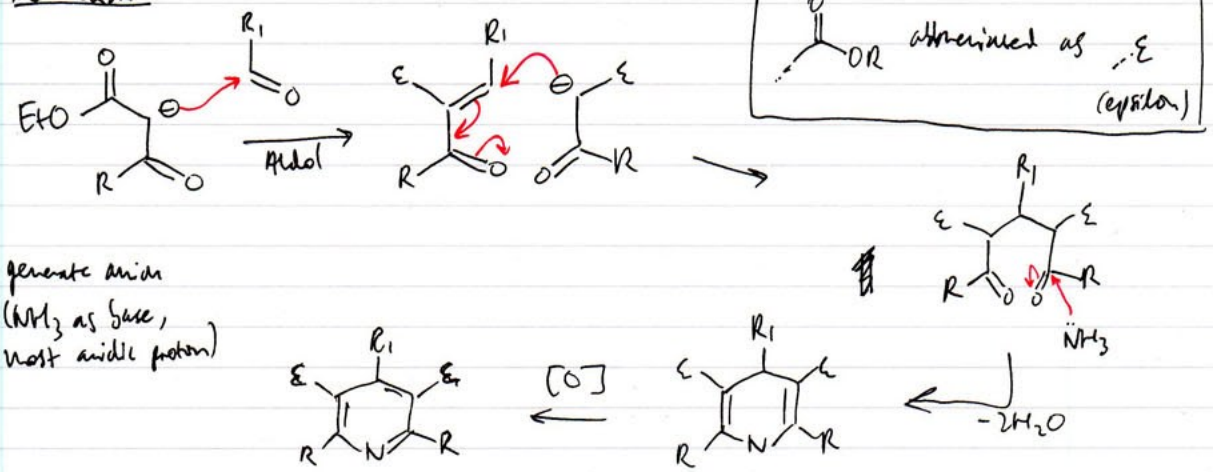
Very simple (operationally), gives every single position on Py ring functionalised. But if you only want one pos^n functionalised, it's a problem.



β-keto ester

useful as drugs and modern NADH mimics.

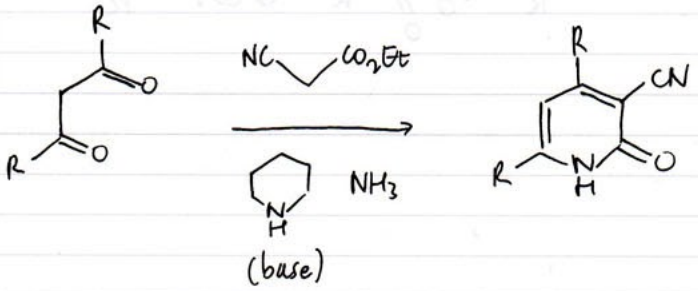
Mechanism



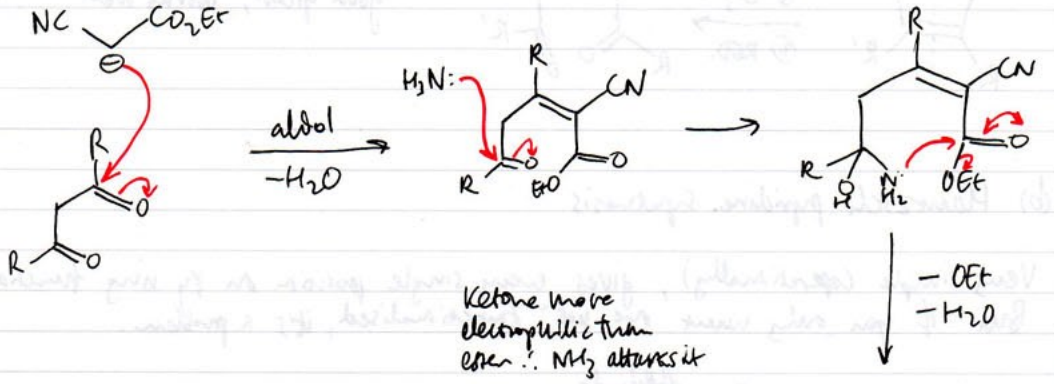
generate anion
(NH_3 as base, most acidic proton)

(c) Guareschi-Thorpe

An incredibly useful rxn, technically a pyridone synthesis.



can convert to pyridines or to all sorts of other things



ketone more electrophilic than ester ∴ NH_3 attacks it

if you replace cyanoester with amide,

avoid necessity for ammonia.