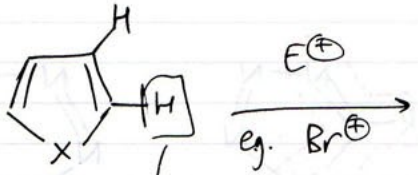
8/11/2010 KIBM - Heterocycles II

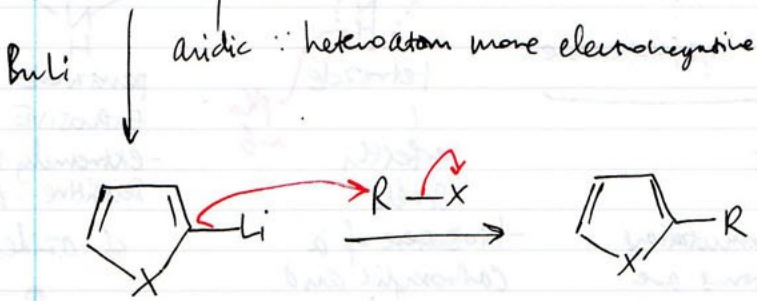
- Read second year notes - third year material carries on from them.
- 90% of small-molecule drugs are heterocyclic

X = O : furan
X = NH : pyrrole
X = S : thiophene

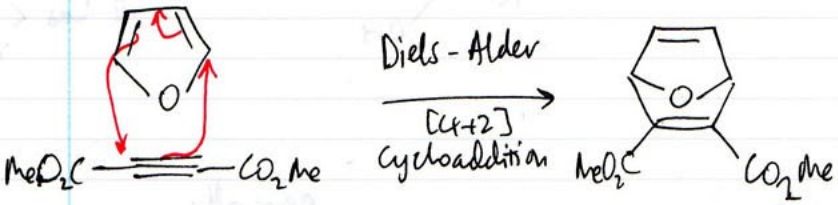
aromatic, 6π electrons
(Hückel's rule: (4n+2) π electrons)

π-electron-rich heterocycles
very reactive to electrophilic substitution (pyrrole ~ 10^7 x more reactive to EAS than benzene - benzene requires Br_2 + catalyst + high T whereas pyrrole brominated in all positions at room temp.)





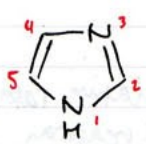
furan less aromatic than pyrrole ∴ can do other reactions:



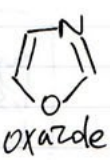
- ∴ heterocycles can be useful building blocks for making more complicated molecules.

Azoles

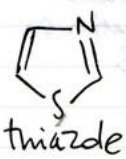
1,3-azoles



imidazole
- of huge importance to life on Earth
- Nature's base - mops up $H^⊕$ in enzymes.
- part of histidine



oxazole



thiazole - eg. in zantac

these are all important in drugs as analogues of imidazole in histidine

1,2-azoles

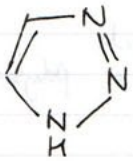
pyrazole

isoxazole

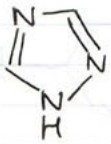
isothiazole

lots of fairly stable heterocycles containing metals (metallocycles) and most main group elements.

Others - all of these have been made.



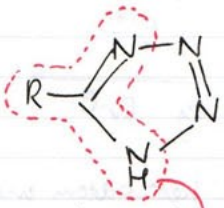
1,2,3-triazole



1,2,4-triazole

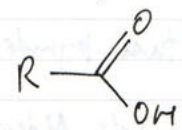
triazoles

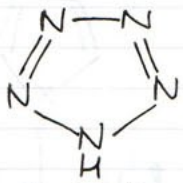
many complicated permutations if one or more N atoms are replaced by O or S ∴ we'll concentrate of 1,3- and 1,2-azoles



tetrazole
/
perfectly stable
- bioisostere of a carboxylic acid

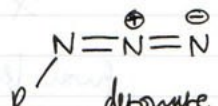
pKa ~6





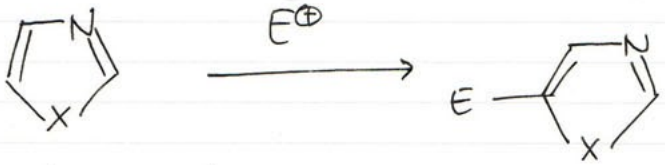
pentazole
EXPLOSIVE
- extremely shock sensitive - detonates

cf. azides



detonate if R has < 6 carbons

Reactivity.



complicated by reaction on N3

deactivated ring
- reversible but complicates reactions
- slower, uses more energy.

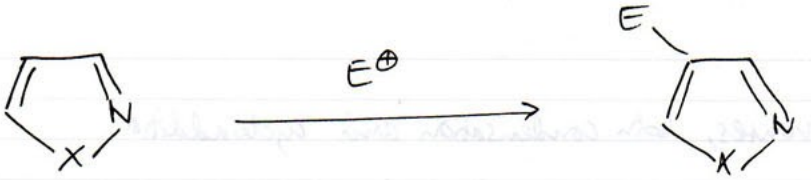
generally get clean reaction on C5

but less reactive than pyrrole

pyrrole	10^7
1,3-azoles	10^5
benzene	1

~ relative rates of reaction.

work out why C5 (out of C2, C4, C5) draw out resonance forms



generally reacts at C4.

X = N, O, S Reaction at other positions leads to highly unstable intermediates.

C3 and C5 substitution give unstable resonance forms. C4 is the lesser of three evils.

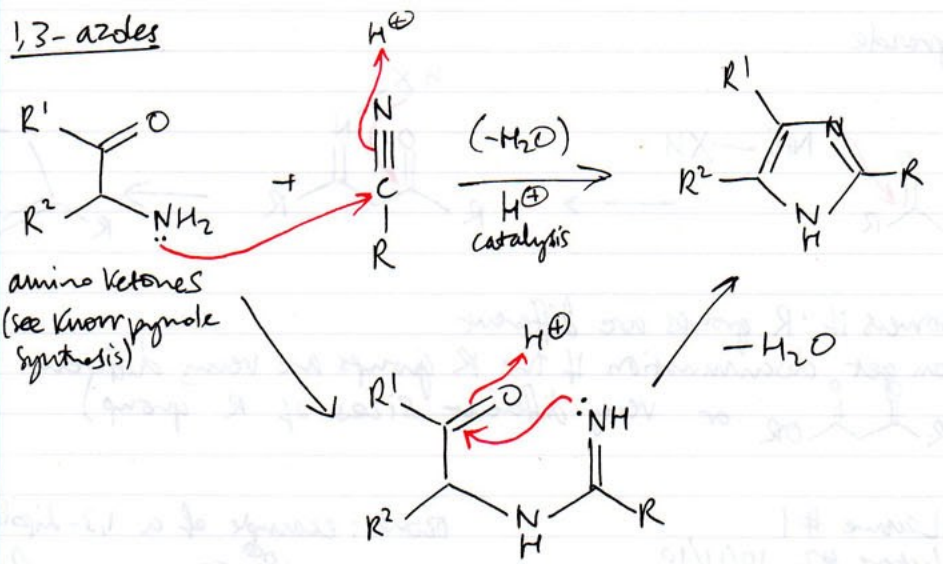
(c.f. pyridine – 2nd year)

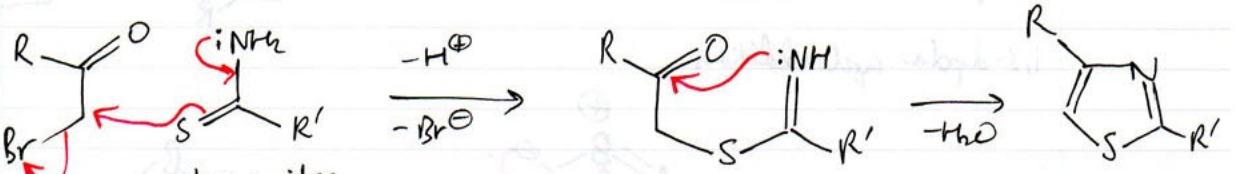
There are a number of textbooks given in the yearbook if you want to know all the different ways of making the many different substituted azoles. We'll focus on just a few.

Synthesis of azoles

Many specialised routes!

1,3-azoles



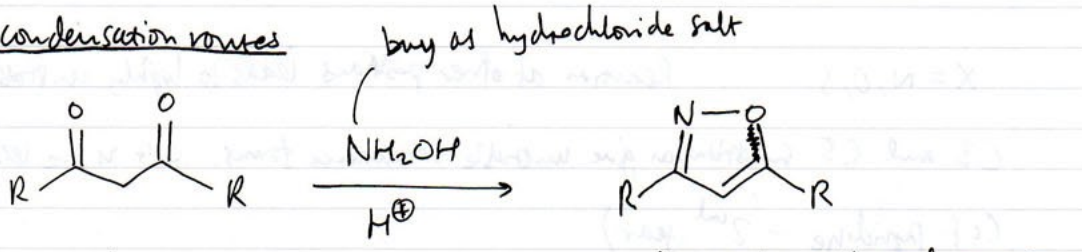


thioamides
- smell of burnt rubber but great S nucleophiles

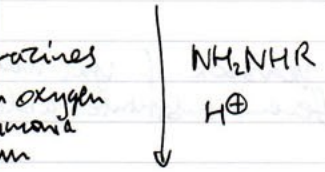
1,2-azoles

Lots of nice routes, both condensation and cycloaddition.

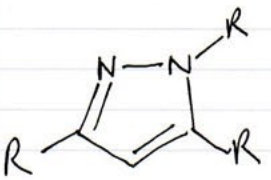
(a) condensation routes



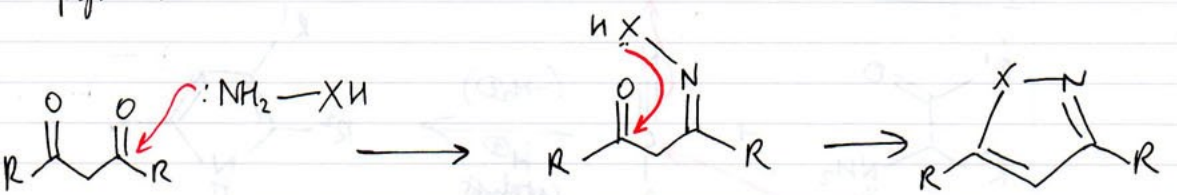
hydrazines react with oxygen to form ammonia and steam



to predict regiochemistry, just consider the mechanism.



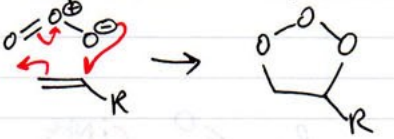
pyrazole



get isomers if R groups are different
you can get discrimination if the R groups are very different (e.g.  or very different sizes of R group)

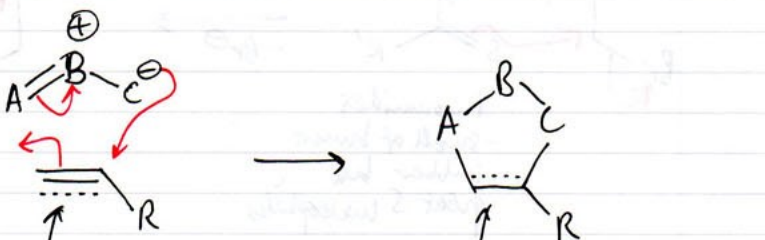
end of Lecture #1
Lecture #2, 10/11/10

ozone : example of a 1,3-dipole



(b) cycloaddition routes

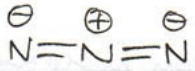
1,3-dipolar cycloadditions

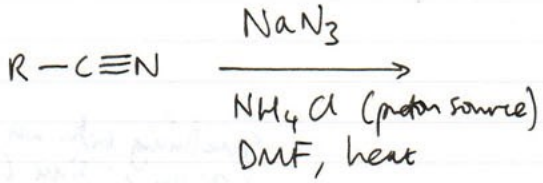


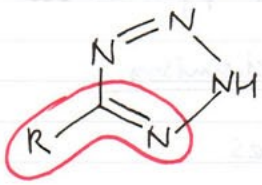
double or triple bond

double or single bond

azide ion as a 1,3-dipole :

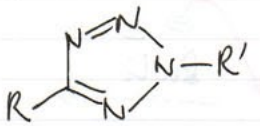






"Click Chemistry"
K. B. Sharpless.

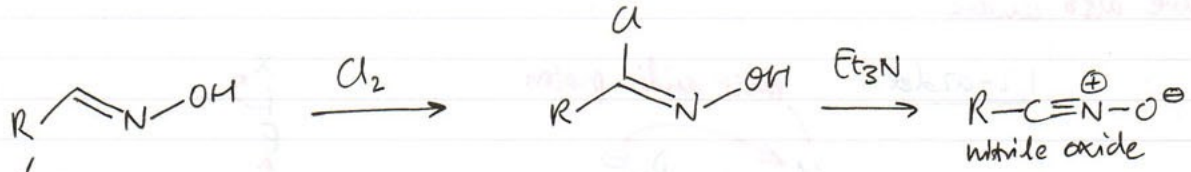
can also use $R'-N_3$ ⟶



useful route to tetrazoles.

biochemists use click chemistry to attach tetrazoles to DNA.

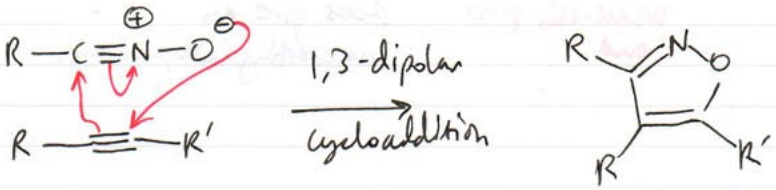
Nitrile oxides



easy to make from aldehyde

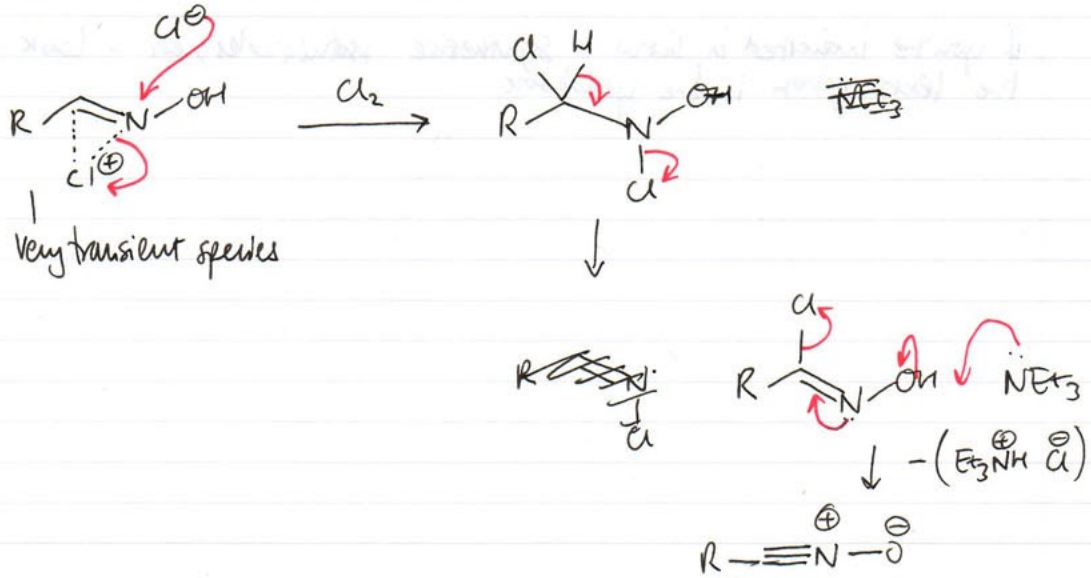
nitrile oxide

a very reactive 1,3-dipole. Keep in solution otherwise it polymerises.



isoxazole

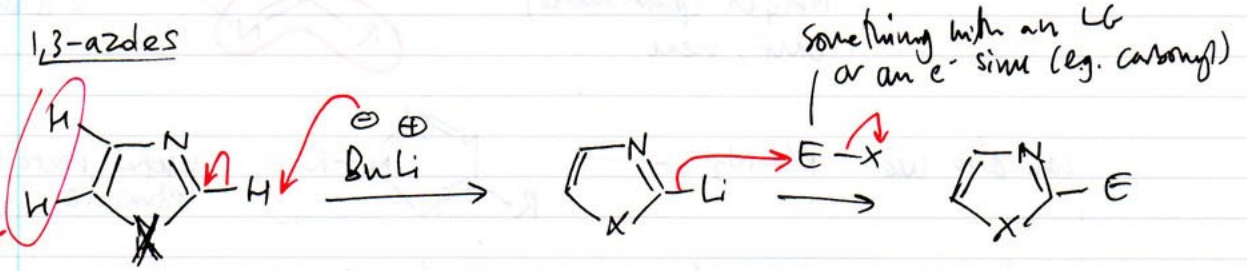
Kißlich's wonking mechanism of oxime chlorination



There are a few direct functionalisations of azoles but they're more limited than for pyrroles etc.

Anion chemistry

1,3-azoles

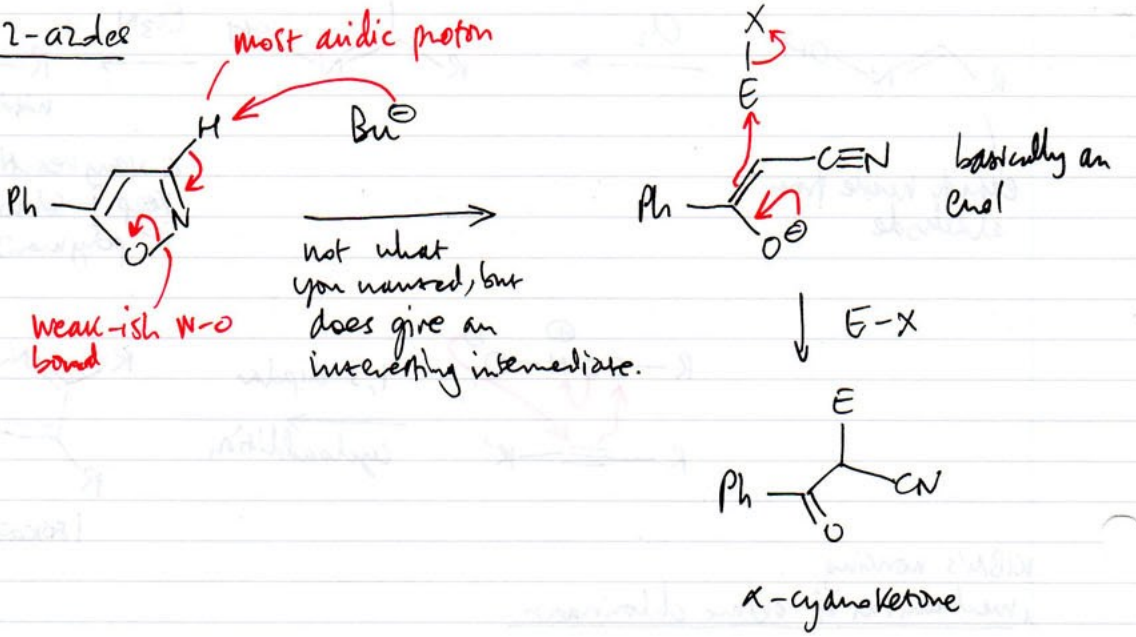


X = NH, O, S

generally this rxn works pretty well, but...

Caveat: these hydrogens are also acidic

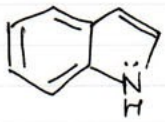
1,2-azoles



if you're interested in how to synthesise isothiazoles, etc – look up in the texts given in the yearbook.

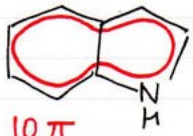
Bicyclic Heterocycles
Indoles and Quindines

Indoles

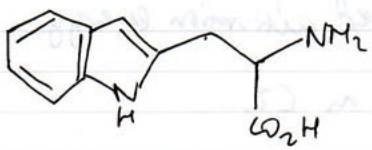


π-excessive – both pyrrole ring and benzene ring very reactive

aromatic – 10 π electron system
$(4n+2$ [Hückel$]$ $\therefore n=2)$

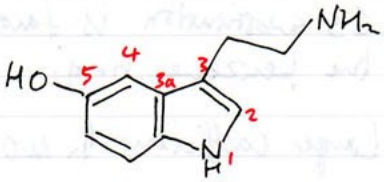


10 π
smeared over both rings

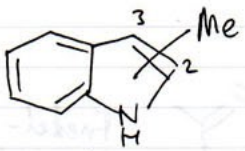


tryptophan (essential amino acid)

In schizophrenia, may get accidental polyhydroxylation of tryptophan to mescaline-type molecules, i.e. powerful hallucinogens



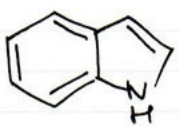
5-hydroxytryptamine
(serotonin)
important neurotransmitter in the brain – essential for the right concentrations at the right time for mood – implicated in depression



skatole
(either 2-methyl- or 3-methylindole)

} stinks, smells of incredibly intense dog poo clings to your clothes – if you get a project using this, change projects!

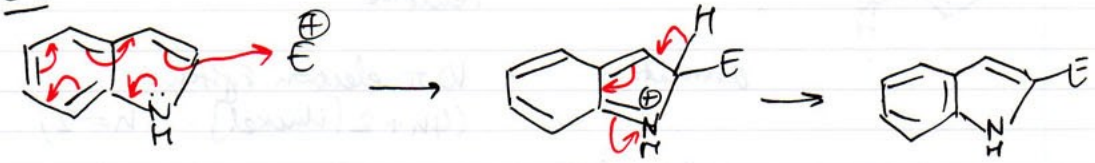
Indomethacin – NSAID, since 1960s, v. useful.



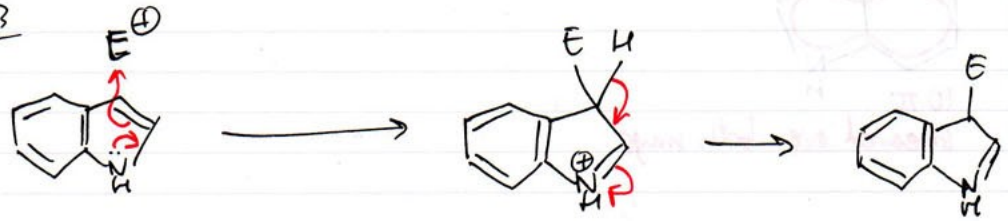
the chemistry of indole is a mixture of that of benzene and of pyrrole, but the pyrrole part dominates.

Electrophilic substitution

C2



C3

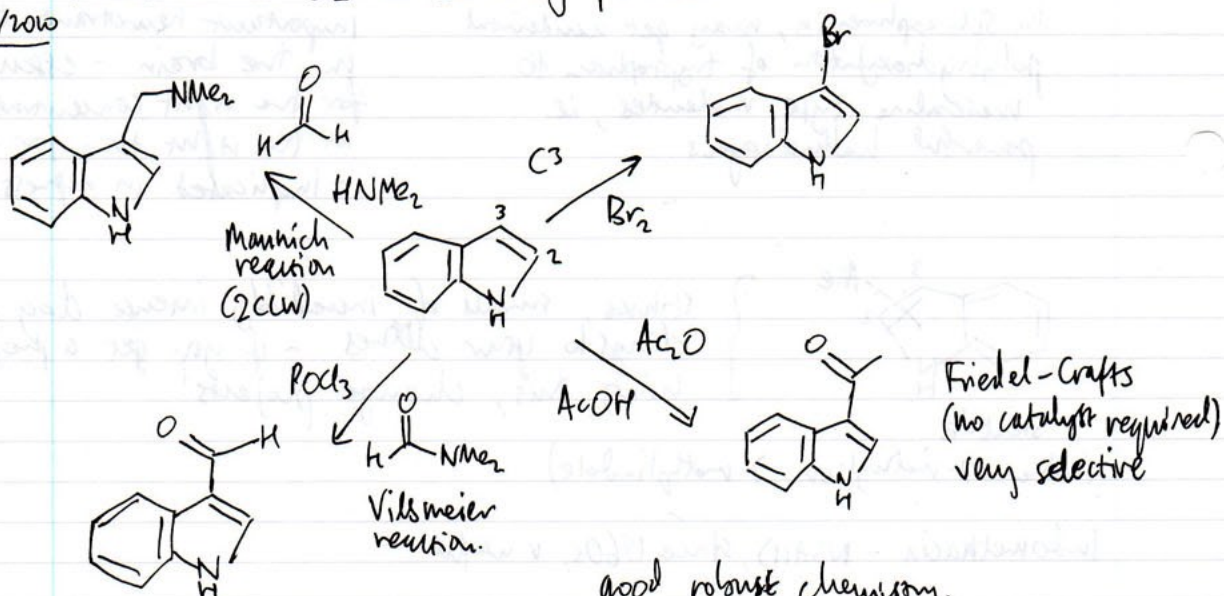


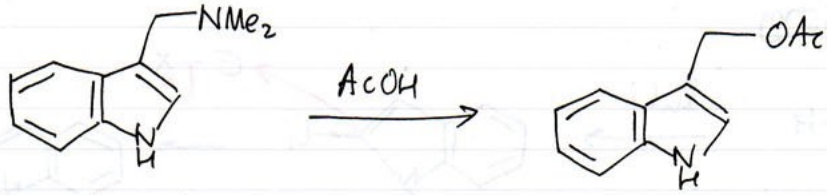
C3 substitution is favoured because you preserve the aromaticity of the benzene ring. C2 has greater activation energy.

Larger coefficient (in HO) on C3 than on C2.

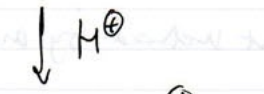
$E^{\oplus}$ adds to C3 first, but product formed is still reactive, so further substitution at C2 is certainly possible.

11/11/2010

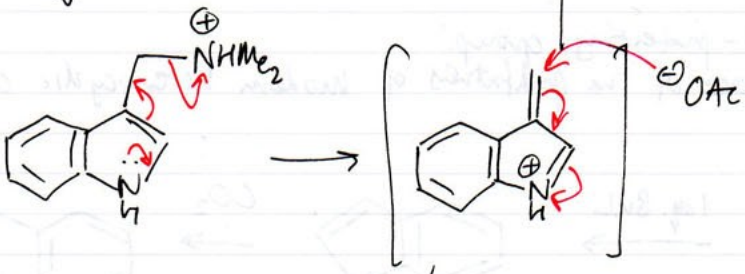




Mannich product - useful store, you can liberate other products from it

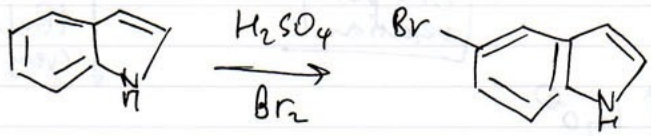


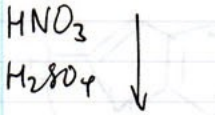
Can use HCl to get the chloride, and so on.

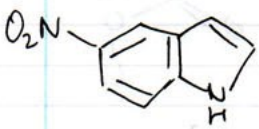


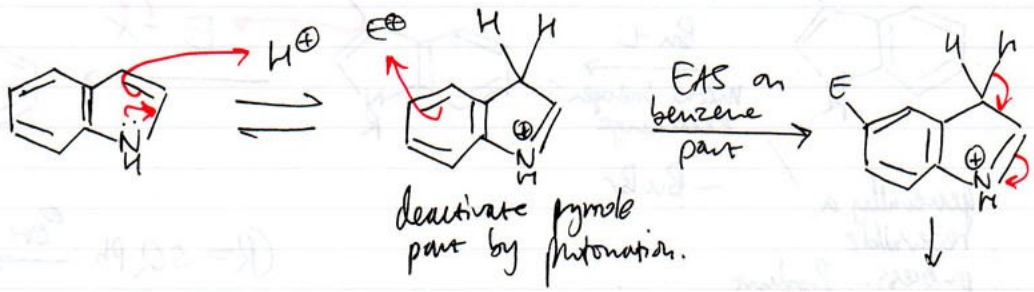
Mannich product is effectively this cation in a bottle.

Strong acid.

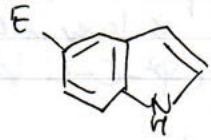




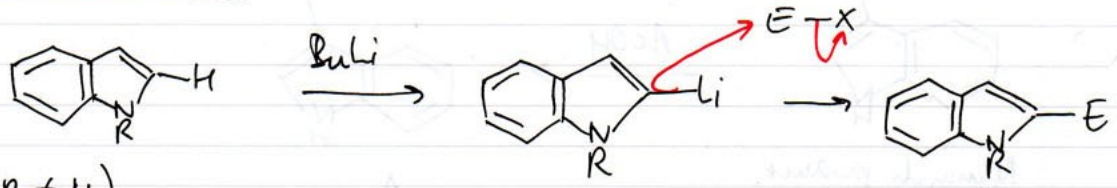




deactivate pyrrole part by protonation.



Anion chemistry

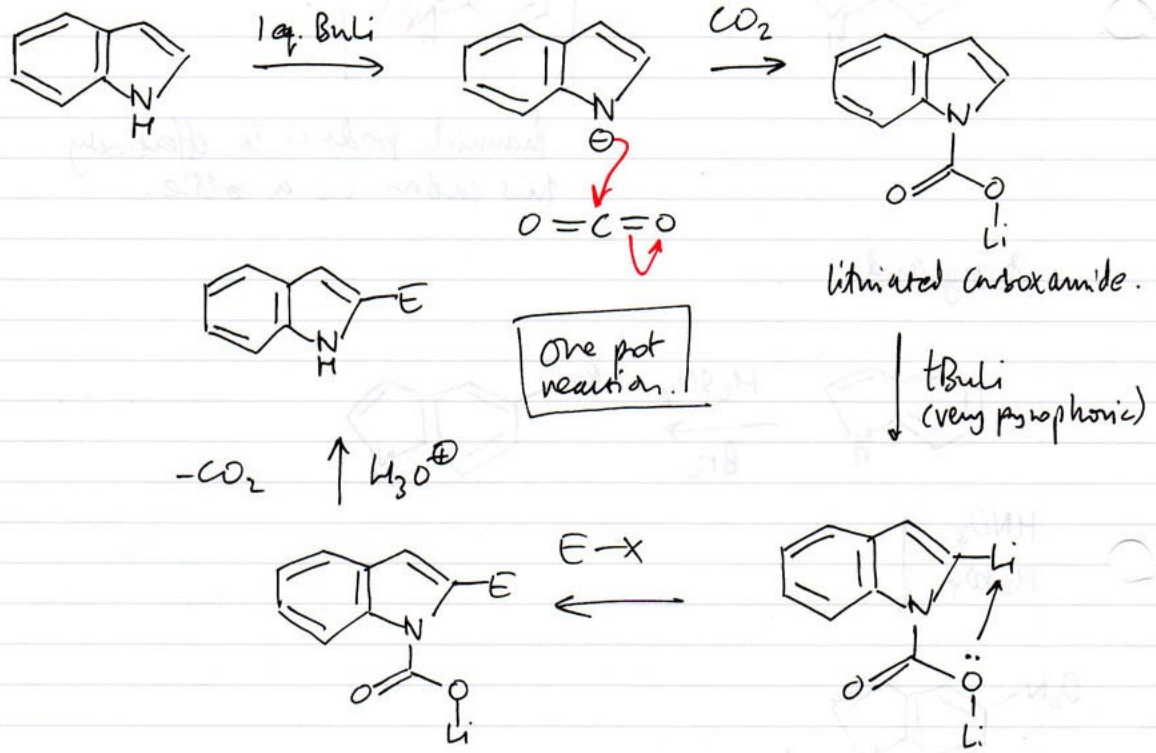


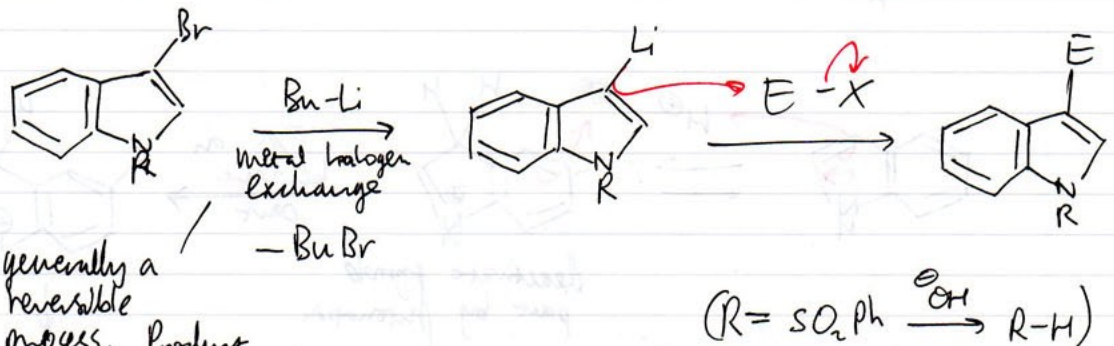
(R ≠ H)

best route into C2 substituted systems from parent indole

If you need R = H, need to use a different method by an English chemist:

Removable N-protecting group.
Katritzky - one of the godfathers of modern heterocyclic chemistry.





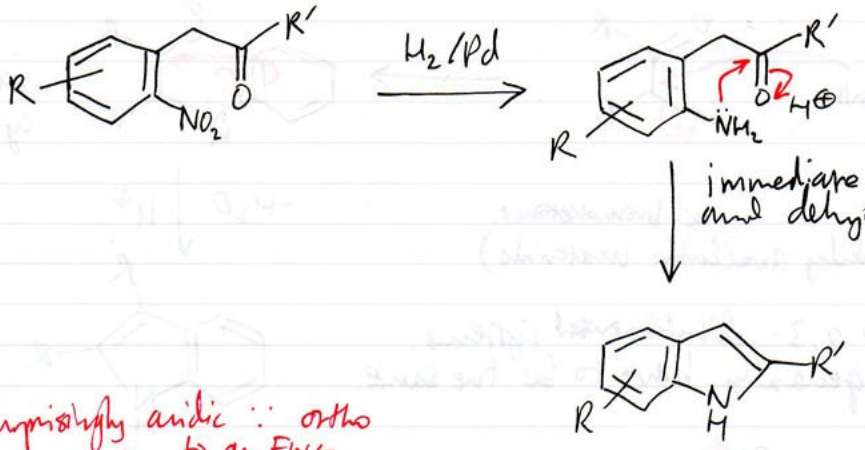
generally a reversible process. Product is lower in energy (sp^2–C–Li better than sp^3–C–Li)

(R = SO_2Ph $\xrightarrow{\ominus OH}$ R–H)

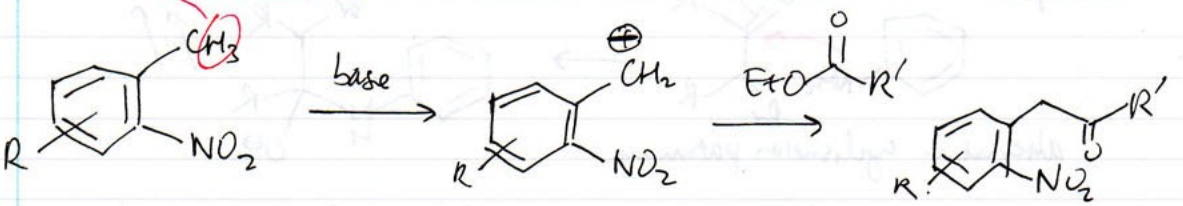
Synthesis of indole rings.

Most early heterocyclic chemistry classics are German or Swiss.

(a) Reissert synthesis.

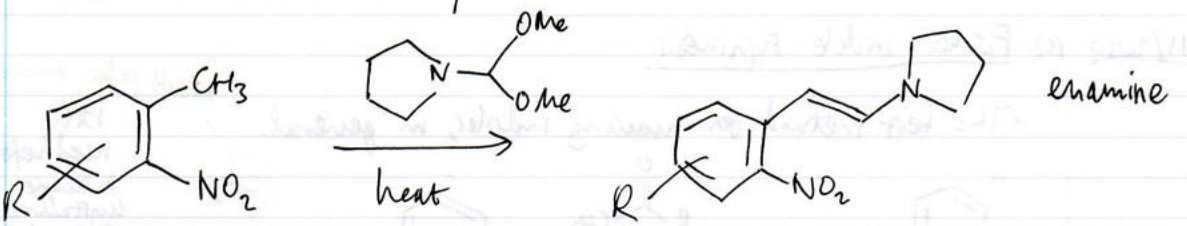


surprisingly acidic ∴ ortho to an EWG



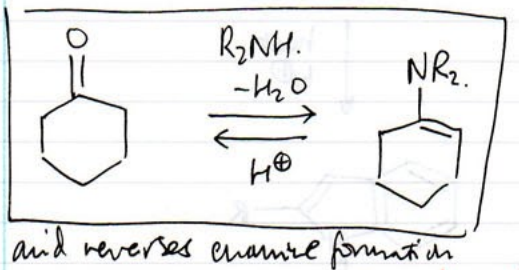
Leimgruber modification.

essentially an acetal of an amide

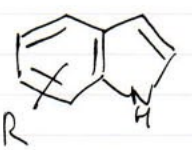


don't isolate enamine, one-pot rxn.

slightly acidic conditions $H^{\oplus}$, Pd/H_2

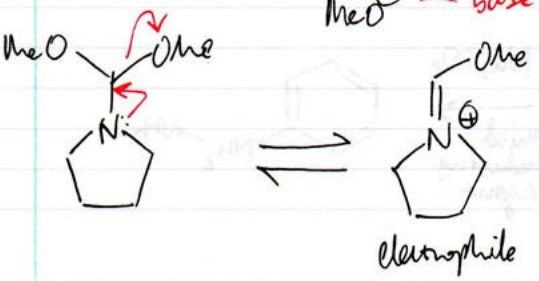


acid reverses enamine formation



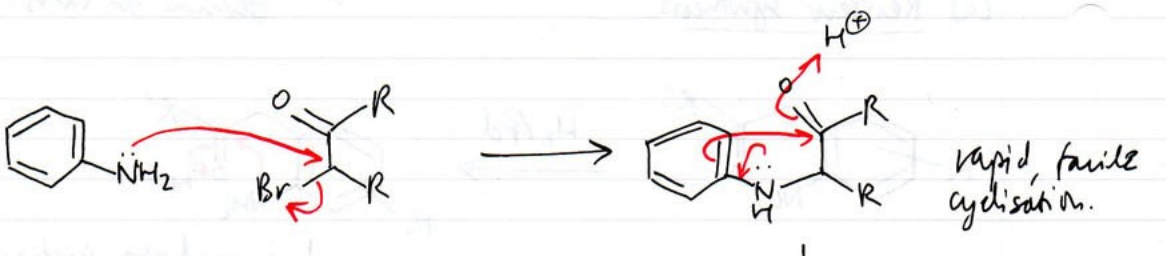
fill in the gaps at home!

$MeO^{\ominus}$ — base deprotonates methyl group in situ.



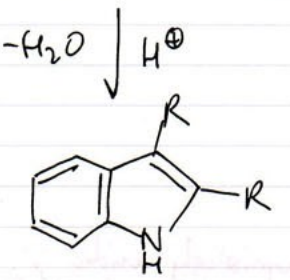
electrophile

(b) Bischler reaction.



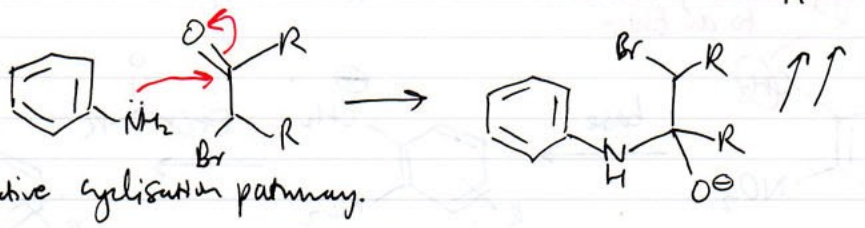
rapid, facile cyclisation.

anilines + α-bromoketones.
(two readily available materials)



limited to 2,3-disubstituted systems.
R groups generally have to be the same.

get...



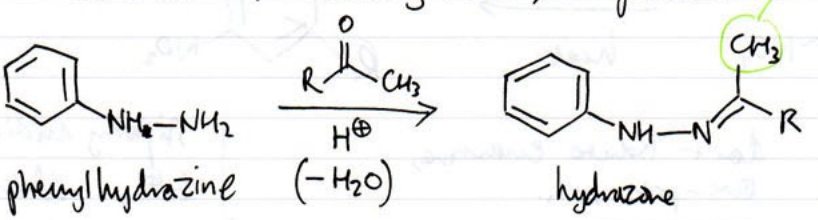
alternative cyclisation pathway.

NP organic workshop next week – KCBM masterclass instead.
Pink sheet – do in advance
Blue sheet – former workshop Qs.

15/11/2010 (c) Fischer indole synthesis

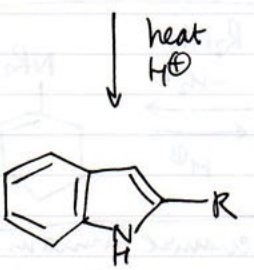
- The best method for making indoles, in general.

needs to be enolisable

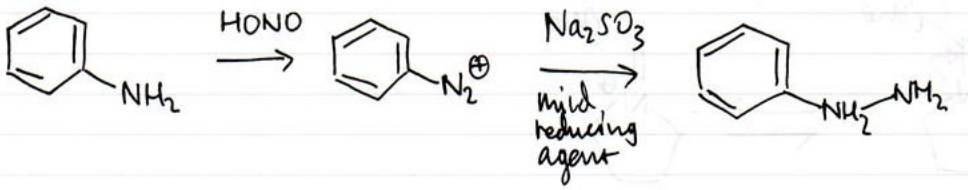


phenylhydrazine (−H₂O) hydrazone

- used before NMR to make crystalline derivatives of ketones – probably how the Fischer indole synthesis was discovered

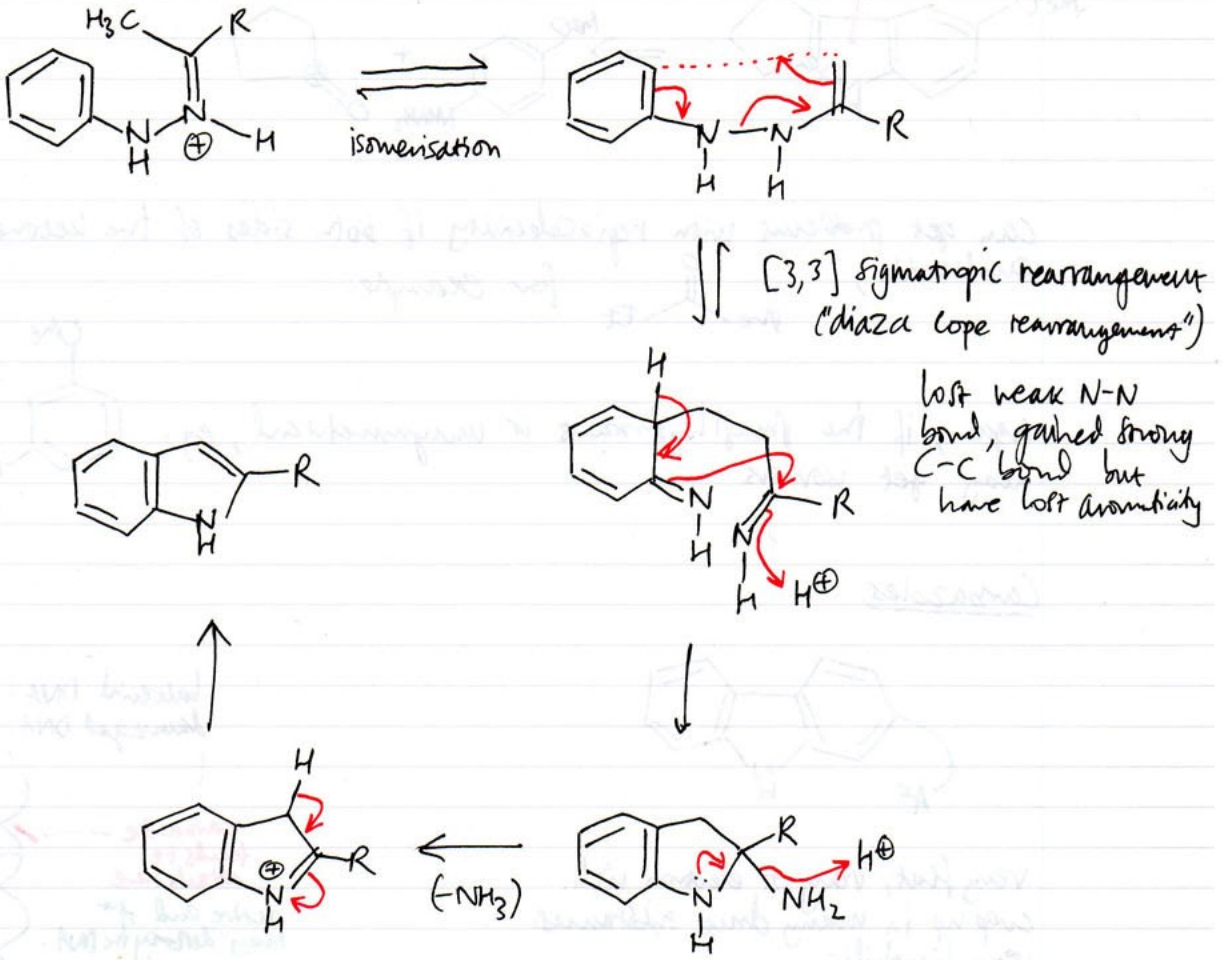


Phenylhydrazine synthesis



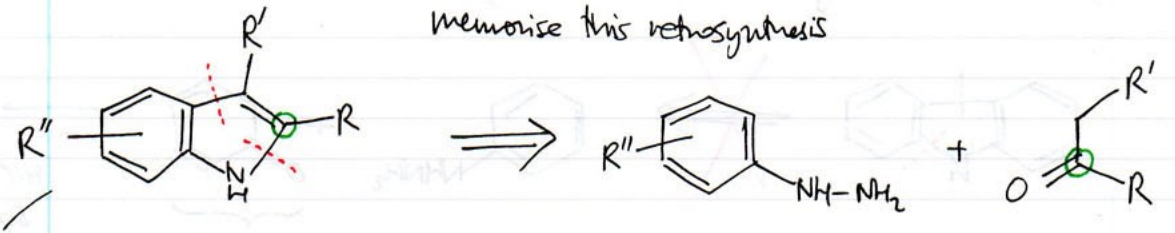
mild reducing agent

Mechanism of Fischer indole synthesis



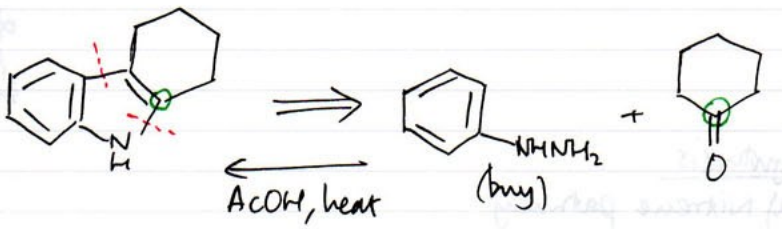
KIBM has slightly abbreviated this mechanism for simplicity - check textbooks for extra steps. Use the mechanism you best understand.

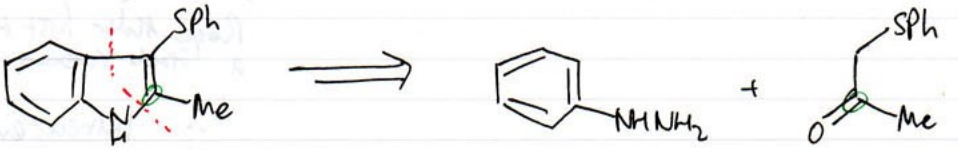
memorise this retrosynthesis

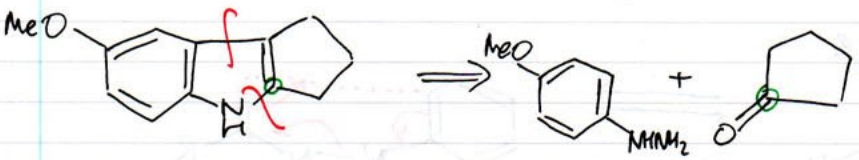


can be heavily substituted up to 3 substituents, need one free)

example:



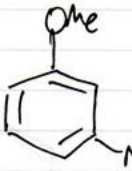




Can get problems with regioselectivity if both sides of the ketone are enolisable,

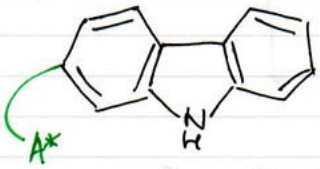
for example.

again, if the phenylhydrazine is unsymmetrical, eg.

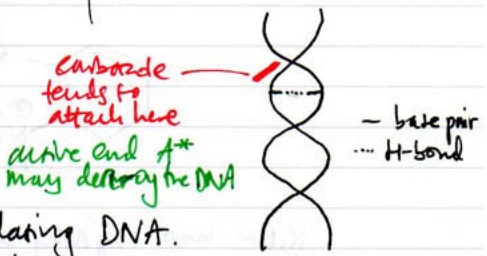


may get isomers

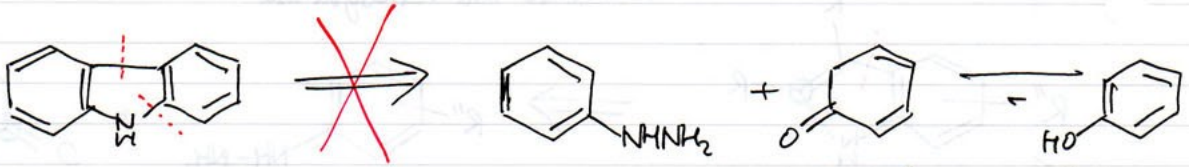
Carbazoles.



bacterial DNA: inferior
damaged DNA: cancer.



very flat, very π electron rich.
crop up in many drug substances.
very lipophilic.
~~very~~ functionalised carbazoles are good at intercalating DNA.
Known for about 15 years that carbazoles intercalate, now working on making them commercially available.



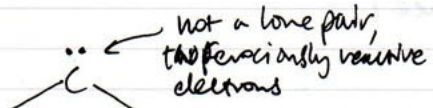
not enough of this form present to be useful.

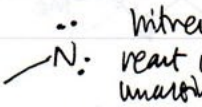
stable, aromatic

99.9%

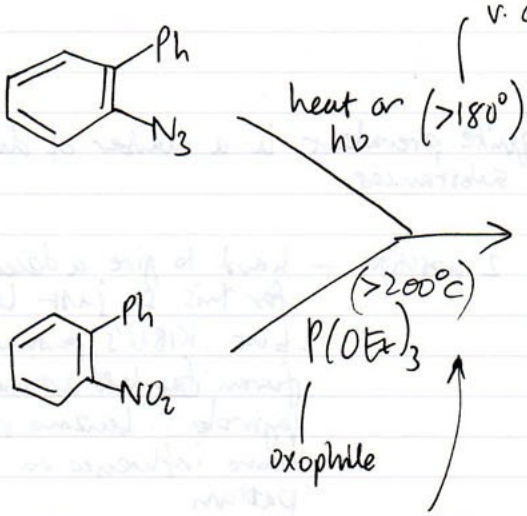
Synthesis

(a) Nitrene pathway



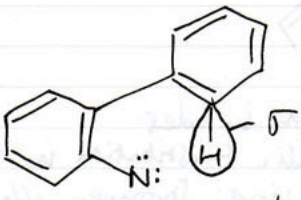


∴ azide, never use on a plant scale v. esoteric reaction!



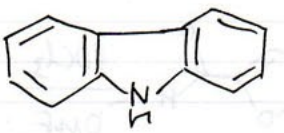
danger of thermal or photolytic detonation

nice six-membered transition state waiting to happen



electrophilic or radical-like

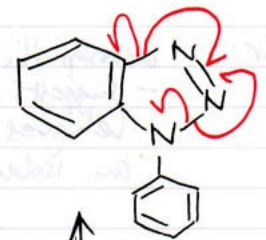
insertion of nitrene N into C-H σ bond (mechanism not well understood.)



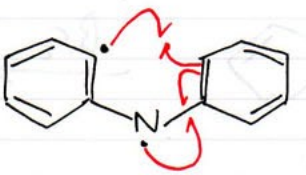
could use microwave reactors to get 200°C or so without the problems of large scale high temp. oil bath methods.

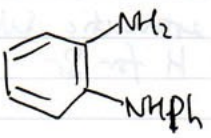
(b) From benzotriazoles: Grabbe-Ullman reaction — really useful.

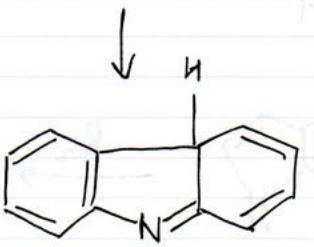
a diazaindole, if you like



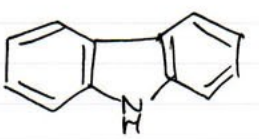
heat (150°C) or hν (300 nm) ($-N_2$)





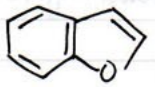


tautomerises to the carbazole



17/11/2010
L5/6

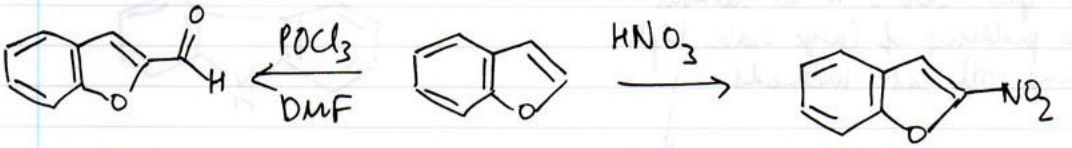
Benzofurans

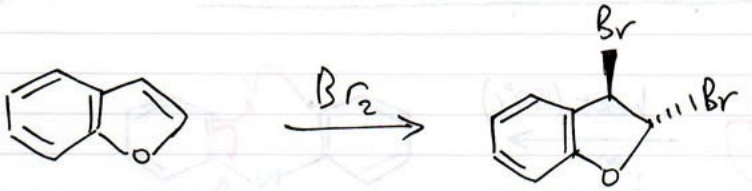


quite prevalent in a number of drug substances.

differ from indoles
electrophilic substitution in the 2 position – hard to give a decent argument for this so just learn it....
benzene ring: stronger effect

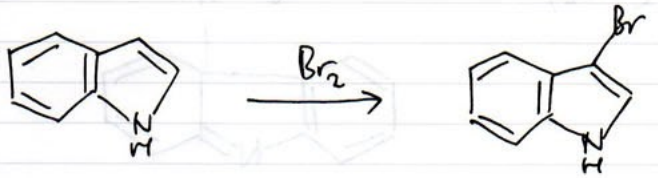
...but KIBM's personal thoughts: furan far less aromatic than pyrrole ∴ benzene ring has more influence on substitution pattern



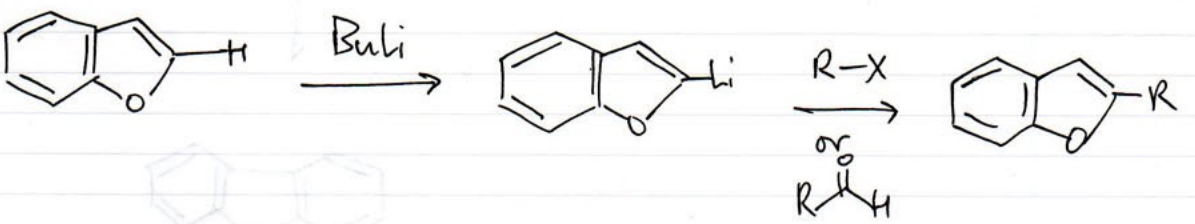


c.f.

electrophilic addition – suggests double bond behaves more like an isolated alkene.



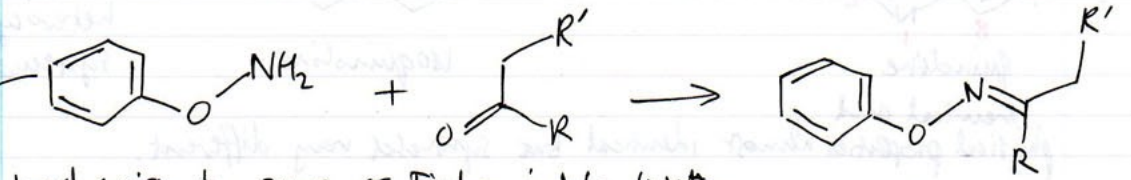
no doubt about it – aromatic substitution of H for Br



Benzofuran syntheses

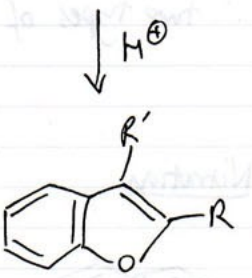
(a) from O-aryl ketoximes. (nicely analogous to the Fischer indole synthesis)

nice route but relies on the availability of this SM - not as readily available as phenoxides

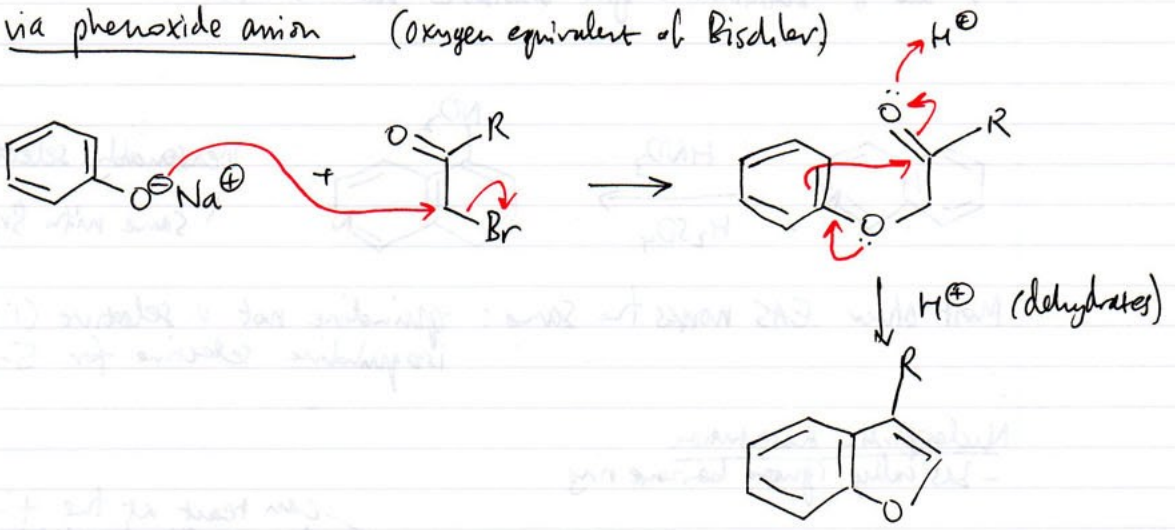


mechanism the same as Fischer indole synth. fill in at home:

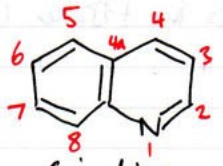
O-aryl ketoxime.



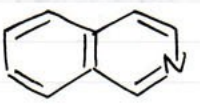
(b) via phenoxide anion (oxygen equivalent of Bischler)



Quinolines and Isoquinolines.



quinoline



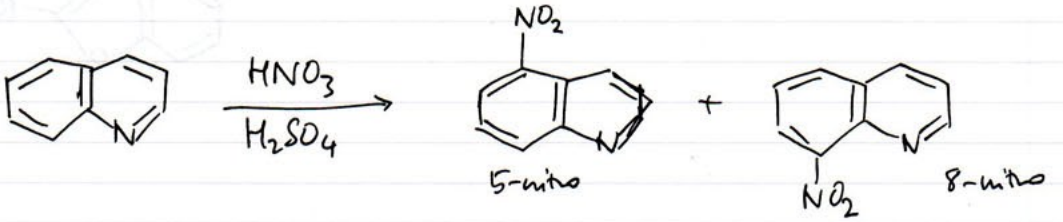
isoquinoline

both π deficient heterocyclic systems

chemical and physical properties almost identical but syntheses very different.

∴ two types of chemistry → benzene ring (mainly electrophilic)
→ pyridine ring (mainly nucleophilic substitution)

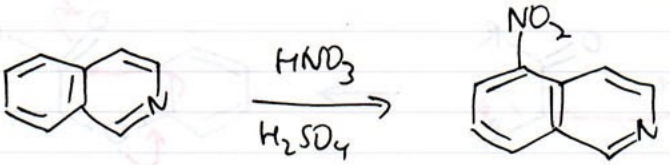
Nitration



1:1

asked why in workshops -
do EAS and get the lowest no of resonance forms (or most stable resonance forms)
→ and 8 substitution give unstable intermediates.

↳ same with $Br_2/H^{\oplus}$ (1:1 again)

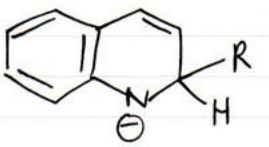


reasonably selective
↳ same with $Br_2/H^{\oplus}$

Most other EAS works the same: quinoline not v. selective (1:1 5 vs 8 subst) isoquinoline selective for 5-subst.

Nucleophilic substitution.

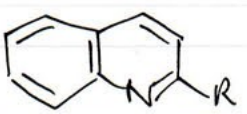
- basically ignore benzene ring

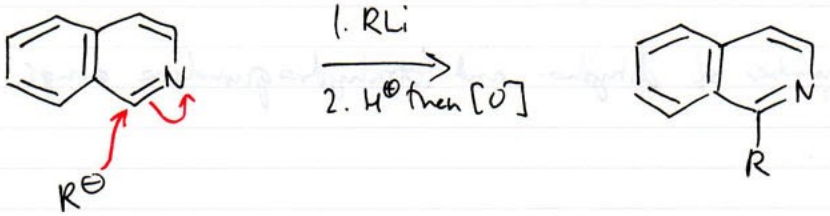


→ can react at the 4-position too but mostly limited to 2-subst.

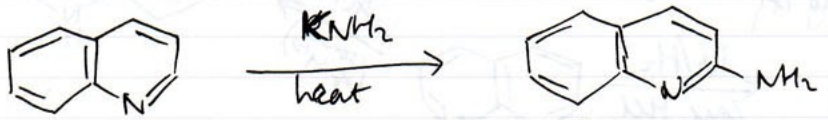
nitrogen stabilises anion

$H^{\oplus}$ then oxidise

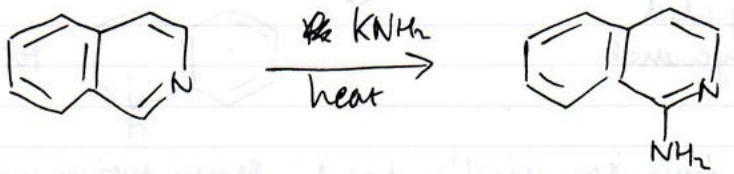


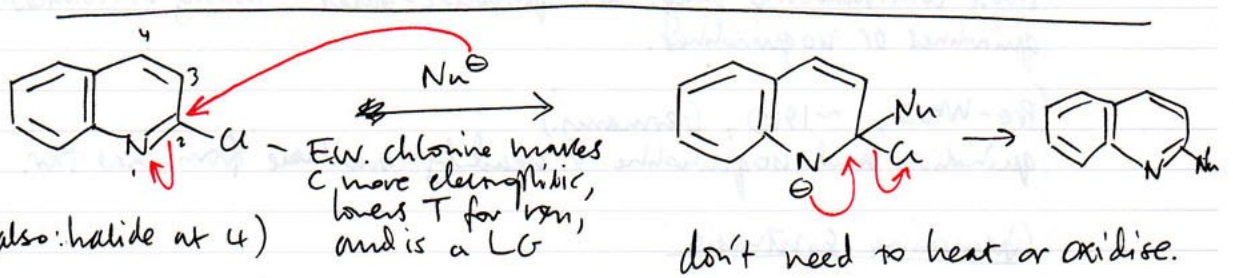


Chichibabin reaction. - more of an industrial process than a lab rxn.



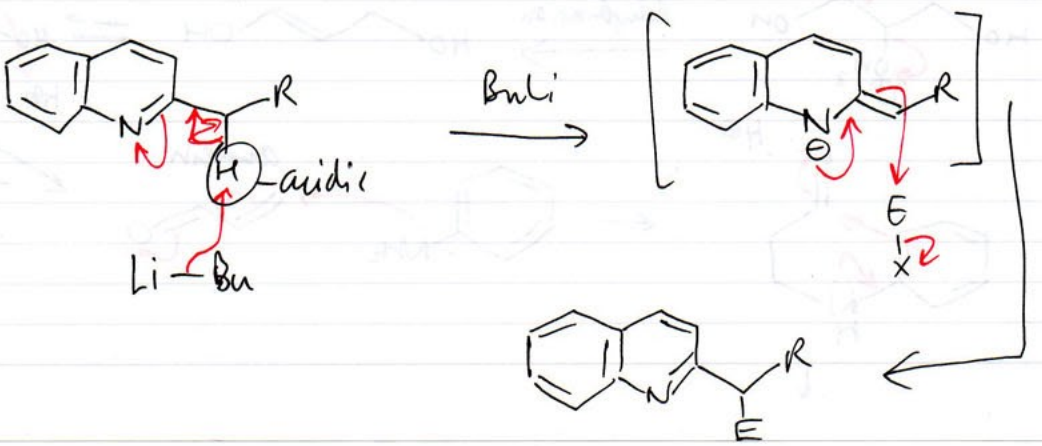
(but not quite as general as for pyridines)





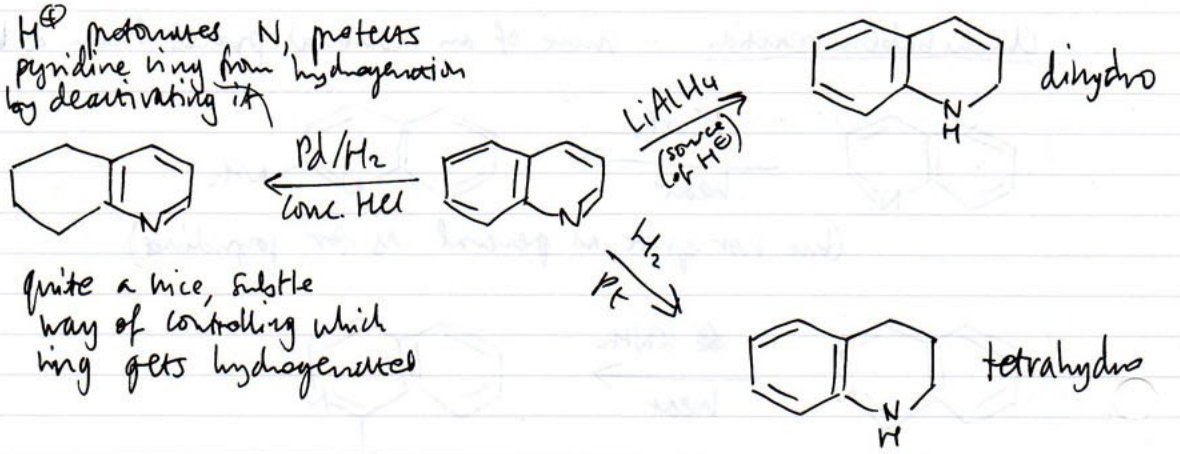
same for isoquinoline:

Anion chemistry (i.e. turning quinoline derivative into an anion so it can react as a nucleophile)



Reduction

There are a number of dihydro- and tetrahydroquinoline drugs.

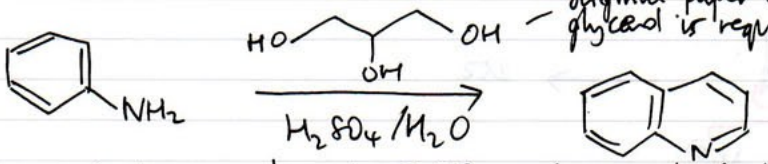


Most antimalarial drugs are quinoline-based. Many anticancer drugs are quinolines or isoquinolines.

(Pre-WWI, ~1910, Germany.)
quinoline and isoquinoline v. readily available from coal tar.

Quinoline Synthesis

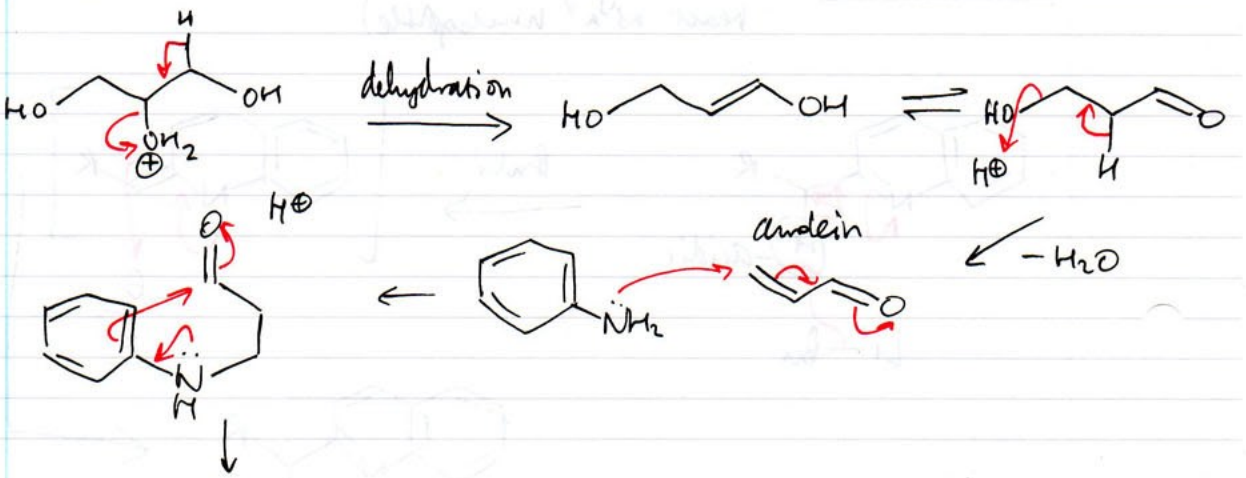
① Skraup Synthesis — Still used today in milder modification.



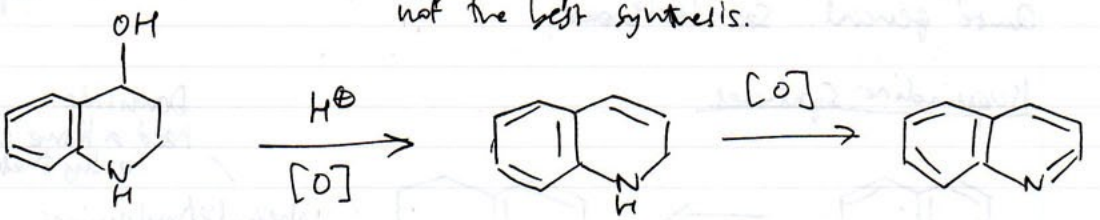
original paper says dynamite-grade glycerol is required (i.e. v. pure)

goes black — previously an industrial process

vicious conditions. heat in $PhNO_2$ — simply a high boiling solvent to 180°C; in air.



requires high temperature and air, so not the best synthesis.



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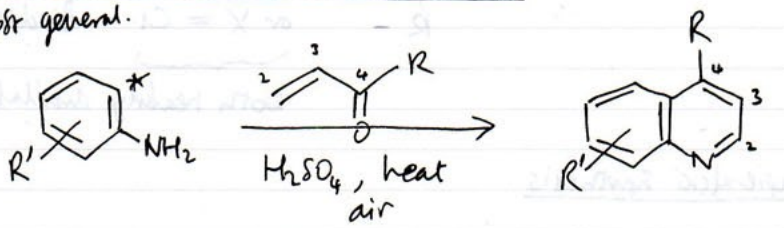
Doebner-Miller modification of Skraup.

1920s-1930s
still used today industrially

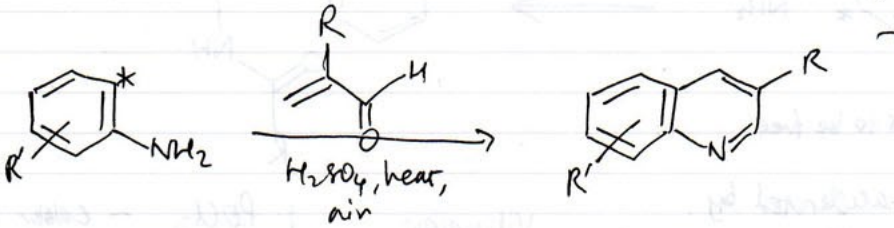
most general.

* free

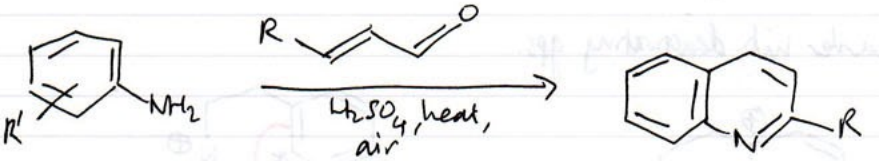


all SMs cheap, readily available, works.

not quite as vicious as the original Skraup, but still not ideal; best suited to larger-scale synthesis.

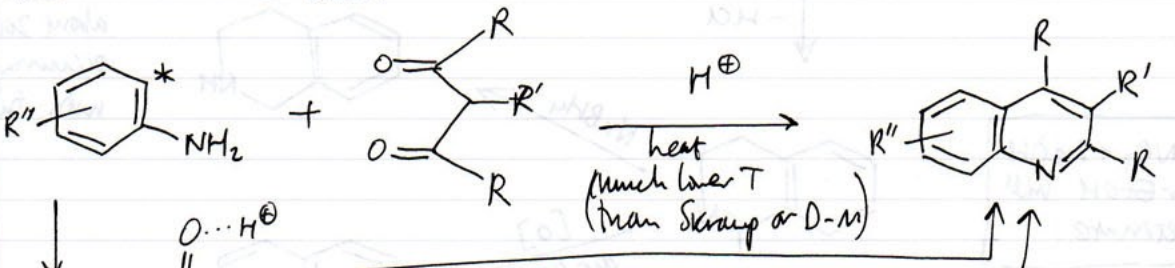


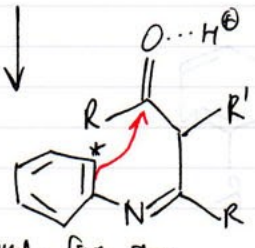
can heavily decorate both aniline and α,β-unsat. carbonyl



⑥ Combes synthesis

Not quite as general as Skraup or Doebner-Miller, but still good, works well on a lab scale.



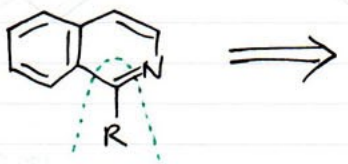


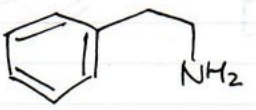
likely first step

Advantages: milder; no need for an oxidation step.
Disadvantage: if dicarbonyl R groups are not identical, get isomers – although control possible if R grps are very different. – electronically – sterically

One quinoline synthesis called the Conrad-Limpet-Knorr, but forms quinolones. Quite general. See textbooks.

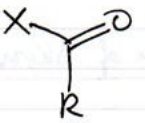
Isoquinoline syntheses.





Downside: need a Home Office licence to buy these - controlled substances

phenylethylamines

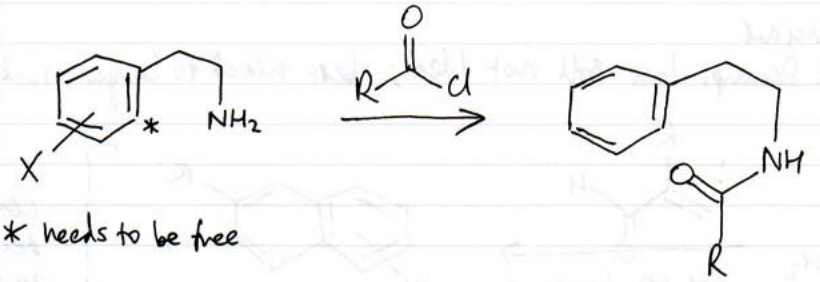


X = H — Pictet-Spengler

or X = Cl — Bischler-Napieralski

both readily available

(a) Bischler-Napieralski synthesis



* needs to be free

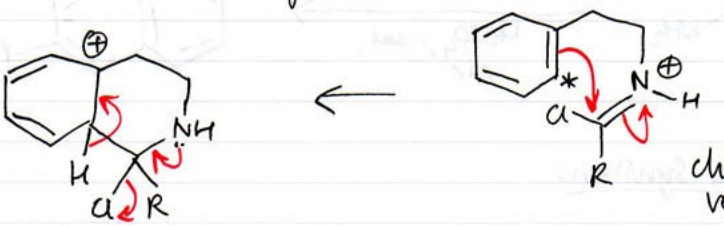
reaction accelerated by activating X groups (ortho/para directing)

much harder with deactivating gps.

Vilsmeier mechanism

$POCl_3$ — easier as liquid

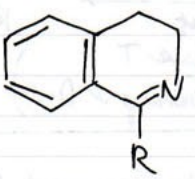
or PCl_5 — tricky - an angry solid



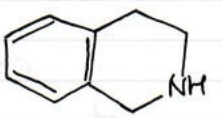
chloroiminium ion. very electrophilic

$-H^{\oplus}$

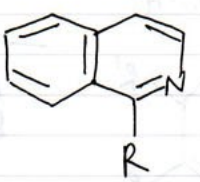
$-HCl$



dihydroisoquinoline



about 2000 naturally occurring compounds with this skeleton.

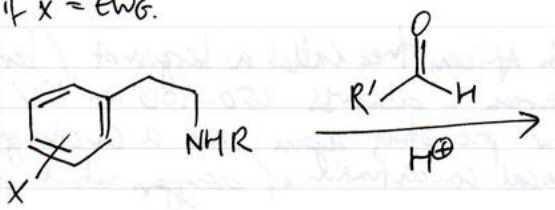


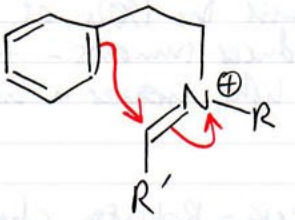
HNO_3 + MeOH or ~~EtOH~~ will detonate

b) Pictet-Spengler

- if you want the tetrahydroisoquinoline, use Pictet-Spengler
- if you want the isoquinoline, use Bischler-Napieralski

Rate of cyclisation is much faster in the Bischler-Napieralski, but still works fine. Both slow if X = EWG.

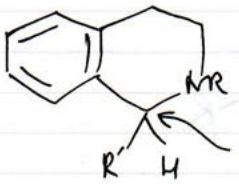




iminium ion (reactive electrophile)

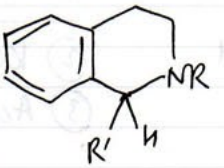
6-endo-trig favoured

Nature makes isoquinolines by this route (more or less). Uses a condensation-cyclisation enzyme.

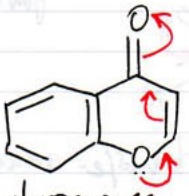


chiral centre

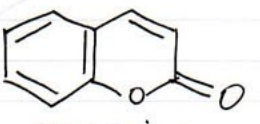
no control in vitro so work is going on to use a chiral acid to try and influence the stereochemistry. No success so far. Enzymes force Ph ring either above or below the plane of the iminium ion.



Chromones and Coumarins.

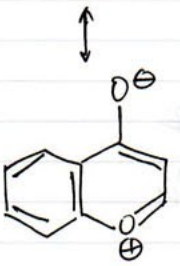


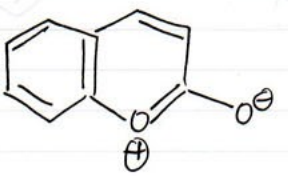
chromones



coumarins

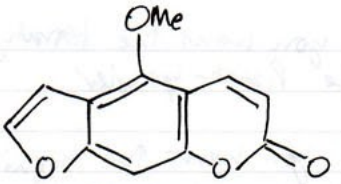
both aromatic by resonance





breakdown of plant pigments, very much influenced by pH, forms these – colour of autumn leaves.

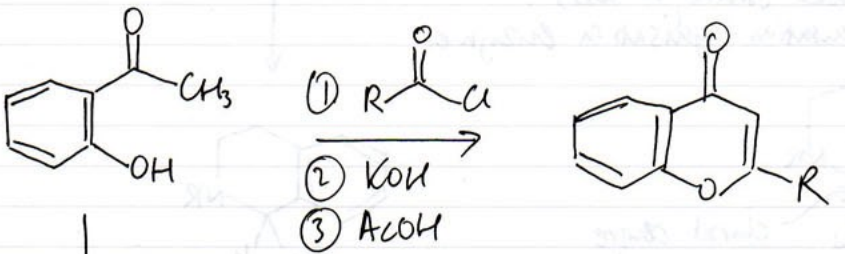
coumarins useful in dye lasers



5-methoxypsoralen.

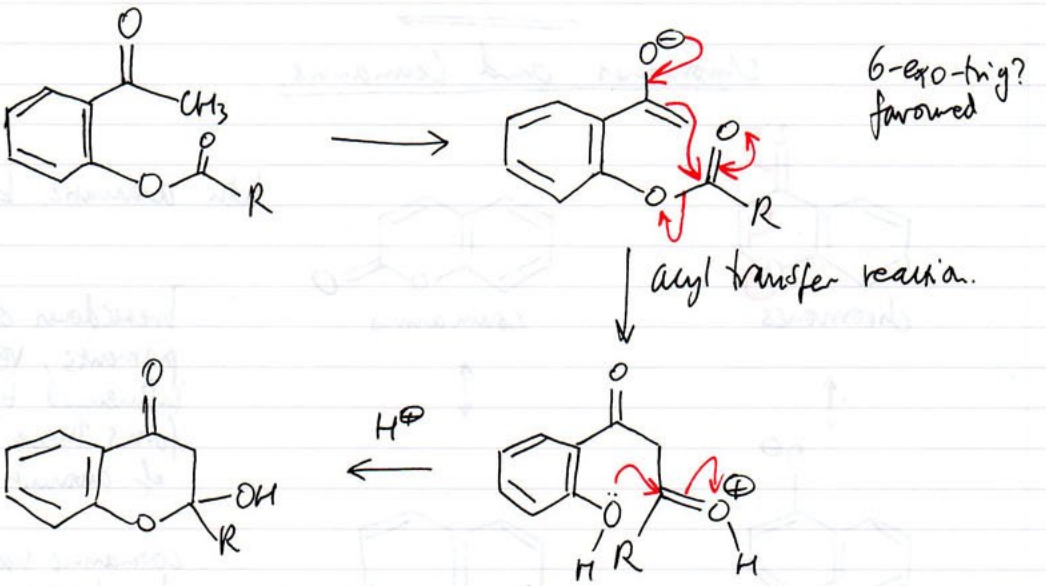
comes from the nut of a south African tree called a bergamot / bergapten.
used until the 1980s as sunscreen - absorbs 250-380 nm UV
but produces tumours - tumour promoting agent not a carcinogen,
absorbs light, creates a high local concentration of oxygen which damages cells

Konstanecki - Robinson chromone synthesis.



a bit like polyketide synthesis.

one pot reaction



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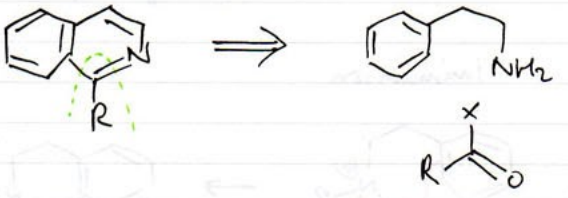
Synthesis of isoquinolines

(Chemistry of quinolines and isoquinolines is essentially the same but synthesis is completely different)

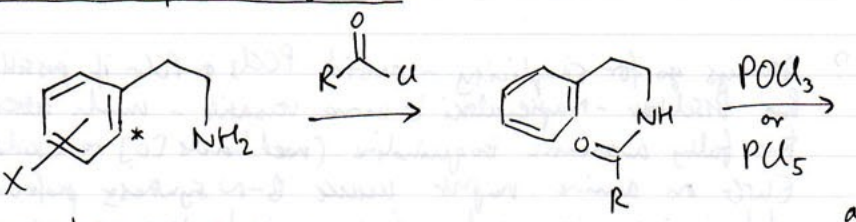
Two very good methods

β-phenylethylamines



X = H or Cl (from OH)

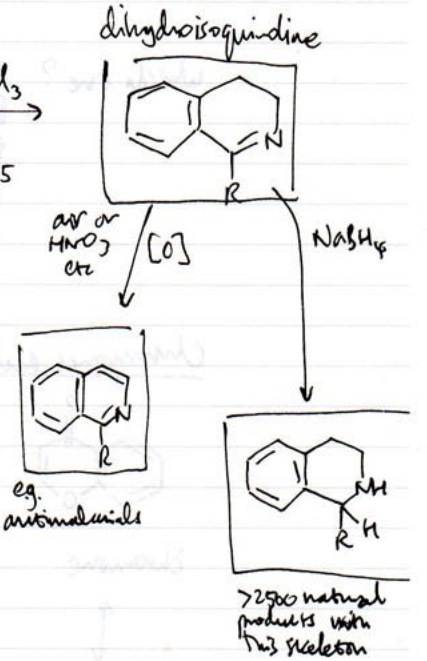
(a) Bischler-Napieralski synthesis.

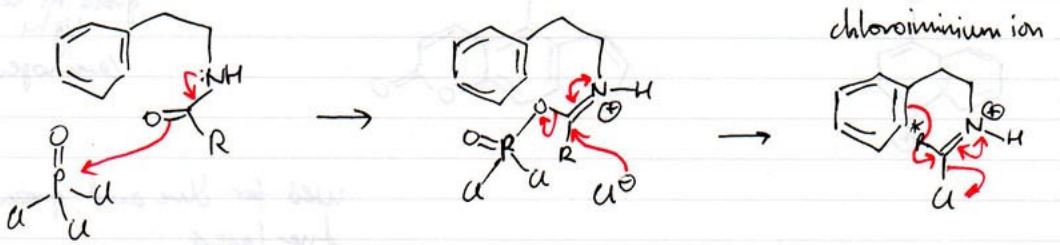


* must have one ortho position free

accelerated by X groups that activate the * position

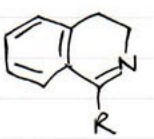
PCl_5 more reactive but more awkward to work with



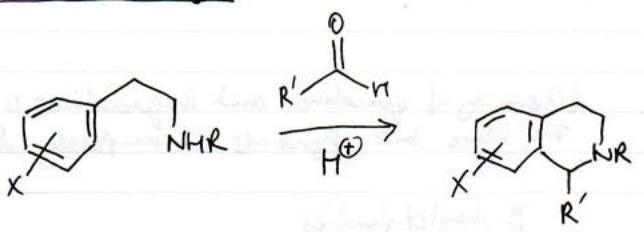


P(v) oxophilic

- like an intramolecular Vilsmeier rxn

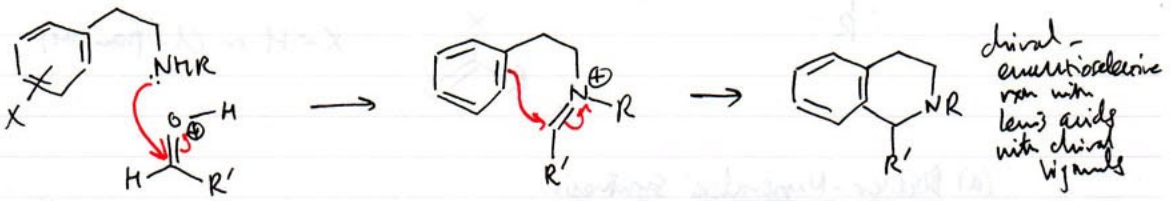


(b) Picket - Spengler



- Simplicity – one step
- protic or Lewis acids
- v. similar to biological version used by nature – enzyme catalysed (acidic enzyme)

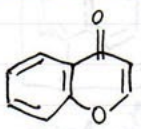
iminium ion



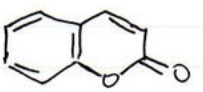
chiral – enantioselective rxn with Lewis acids with chiral ligands

which one? Always go for simplicity – avoid $POCl_3$ or PCl_5 if possible.
But Bischler-Napieralski is more versatile – much better route to the fully aromatic isoquinoline (need harsh [O] to oxidise tetrahydro).
EWG on amine might make B-N synthesis preferable – dehydroiminium ion orders of magnitude more reactive than iminium.

Chromones and coumarins

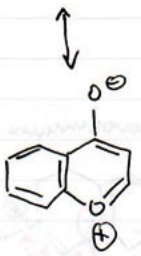


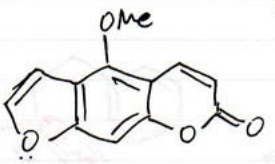
chromone



coumarin

Autumn leaf pigments – no-one really knows why plants do this!

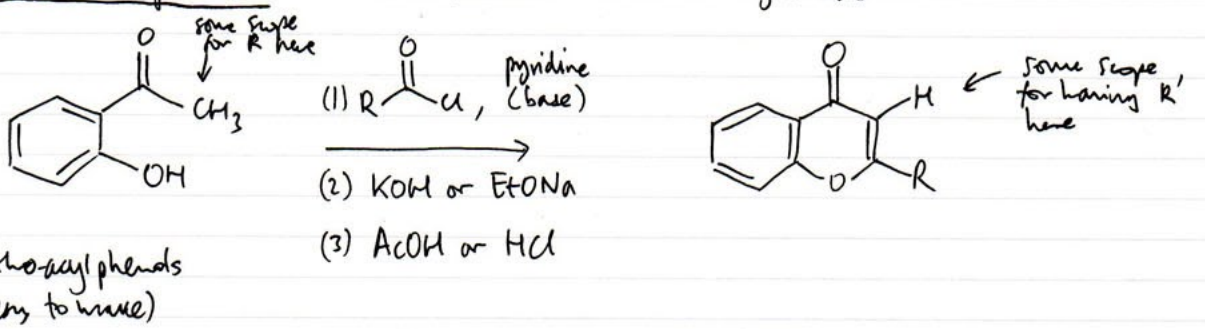




1970s:
5-methoxypsoralen isolated from bergapten – Bergvad sunlotion great at absorbing UV light but carcinogenic!

used for blue and green dye lasers

Chromone synthesis – Kostanecki-Robinson Synthesis



ortho-acyl phenols (easy to make)