

* تفرغ ريكودات وكتوره بين + اهتمامات

راه' ساد يلي حكة نركز عليهم ويلا

حكة ما نركزوا عليهم .

* كل سلاح في حته المطلوب والهدف وأهم المعلومات
يلي ممكن يدجي عليهم بالاعتقان .

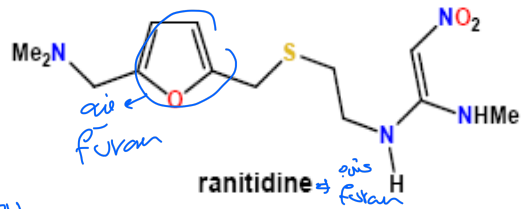
system يكون $rich\ e^-$ (فني بالالكترونات)

PI-EXCESSIVE RING SYSTEMS

الشابتر يلي قبل كينا عن
PI-deficient
يعني ان system فقير بال-
مكافئته ان Pyridine

شابتر اليوم رح غني عن ال
PI-excessive
يعني ان system فني بالالكترونات
ويكون مركبات الخلقات الخاصة
يلي عن heteroatom

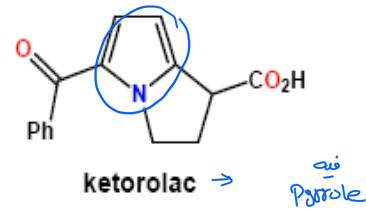
هذول عبارة عن أدوية وتركيبها الكيميائية



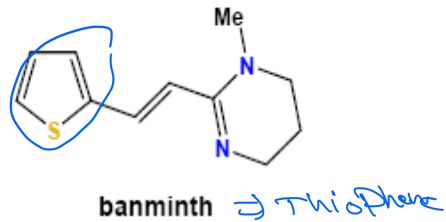
الحقة تبعية - حواء لحواء قرحة المعودة

• **Ranitidine (Zantac®, GSK)** is one of the biggest selling drugs in history. It is an H_2 -receptor antagonist and lowers stomach acid levels – used to treat stomach ulcers

فقد عمل Ranitidine
هنا بالمعدة كنا نحيا بفقر HCl
المعدة Parietal cell - الخلايا هيا
بدونها اشي-تتكونها انة تفترز HCl
من بكتيريا؟ اربابا ان histamine
ال H_2 receptor (2) يلي ان Parietal cell - تفترز HCl
في الدواء هذا يعمل Block H_2 receptor
• **Ketorolac (Toradol®, Roche)** is an analgesic and anti-inflammatory drug



مكن للألم



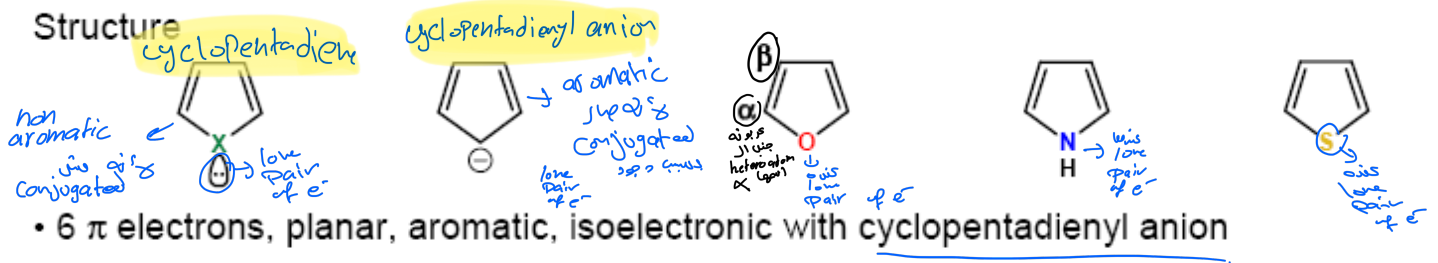
• **Pyrantel (Banminth®, Phibro)** is an anthelmintic agent and is used to treat worms in livestock

حكة
هذول
للذي
فش
للحفظ

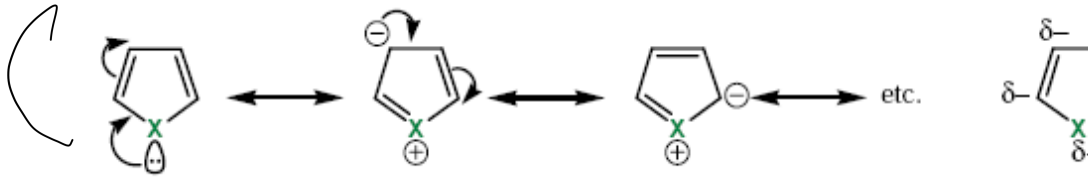
يستخدم بالطب البيطري
لعلاج الديدان القوية المكونة

1. aromatic
 2. conjugated
 3. planar
 4. Hückel's Rule = 1

Furans, Pyrroles and Thiophenes – Structure



Resonance Structures



• Electron donation into the ring by resonance but inductive electron withdrawal

resonance effect
 Ring
 Inductive effect
 Ring

1.35 Å 1.44 Å 1.37 Å O 0.71 D	1.37 Å 1.43 Å 1.38 Å H 1.55 D	1.37 Å 1.42 Å 1.71 Å S 0.52 D
1.68 D O	1.57 D H	1.87 D S

resonance
 hetero atom (N, O, S)
 partially positive
 poor in e⁻
 electrophile
 rich in e⁻
 nucleophile

• O and S are more electronegative than N and so inductive effects dominate

الفكر في السلسلة يلي قبل:

هذا Ring تميزه e^- ولا لا :
هو عامل



Resonance
(يعني e^- للقة، خايف خينة)

Inductive effect
(موسم e^- في السلسلة، خايف خينة)

Pyrrrole (N)

① resonance : قوي $\Rightarrow$ يعزز e^- للقة، ويقلل خينة

② Inductive effect : متوسط $\Rightarrow$ لا يحب كثير من اللقمة -
resonance > Inductive

Furan (O)

① resonance : قوي ولكن أضعف من النيتروجين

② Inductive effect : قوي $\Rightarrow$ قوي من النيتروجين
Inductive > Resonance

Thiophene (S)

① resonance : خفيف

② Inductive : خفيف
توازن بين resonance و inductive

(electrostatic) : resonance 1) σ bond



(electrostatic) : Inductive effect 2) π bond



conjugation (electrostatic) : π bond 3) π bond



معلومات في حال خاسيها : ϕ ile : حب

التركيبات

electrophile

حب للاب

معناه هو موجب

(poor in e^-)

ال

يجعل تفاعل

nucleophilic

substitution

↓

nucleophile

حب للموجب

ال

معناه هو سالب
(rich in e^-)

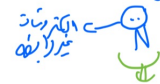
أو يعبر

سالب

لوجود إلكترونات

غير رابطة فيه

مثلا



يعتبر nucleophile

لأنه للموجب

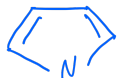
أشياء سالبة

ال

يتحول تفاعل استبدال إلكتروني

electrophilic substitution

Pyrrole



خاصية فيها N

Chemical Properties of Pyrroles

Electrophilic Substitution.

Pyrrole هو
محتلة rich
in (nucleophile)
الكوب
يعمل تفاعل
electrophilic
substitution

A significant feature of the pi excessive

- ring systems is that they are highly reactive to electrophilic species, totally unlike the pi-deficient rings.

كيس

القصير بالالكترونات

2 تفاعل بسهولة مع

electrophile تفاعل
بسهولة مع nucleophile

The reactivity is greater than that of benzenes bearing roughly the same range as found for benzenes bearing electron releasing groups as in aniline.

CH₃

amino

donating

يعمل تفاعل القعات الجاسرية يلي تحتوي هذه hetero
مع electrophile هو أكثر من في ال electrophile
لو أفضت ال benzene حركته مافيه لالكترونات 2 في
تفاعل مع electrophile أكثر وتفرغ من تفاعل electrophile مع hetero

As a result, many useful substitution reactions are known for these heterocycles.

- The greater electron density in these rings accounts for this higher reactivity. The order of reactivity in aromatic substitutions is generally

1

الترتيب من حيث ميل التفاعل electrophilic

pyrrole > furan > thiophene.

(N)

(O)

(S)

تفاعل (محتلة خا فيه نيترو heteroatom)
electrophile مع

تفاعل benzene
electrophilic مع

تفاعل (محتلة خا فيه نيترو heteroatom)
electrophile مع

تفاعل benzene bearing electron releasing
electrophile مع

2

ملخص الامتحان في قوى بالتفاعل electrophilic
الترتيب من حيث القوة بالتفاعل electrophilic

Pyrrrole > Furan > Thiophene > benzene

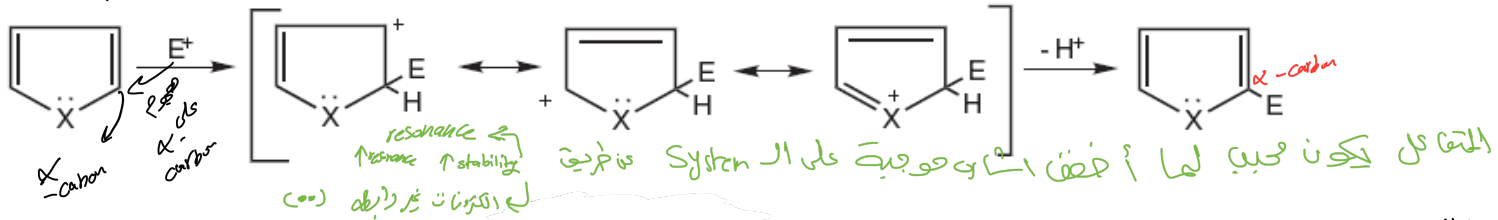
لكن لو انا benzene انا انا benzene انا انا benzene
CH₃ -

أو amino group (e⁻ donating group) 2) في التفاعل electrophilic

في electrophilic reaction انا Pyrrrole انا

Furan انا Thiophene انا

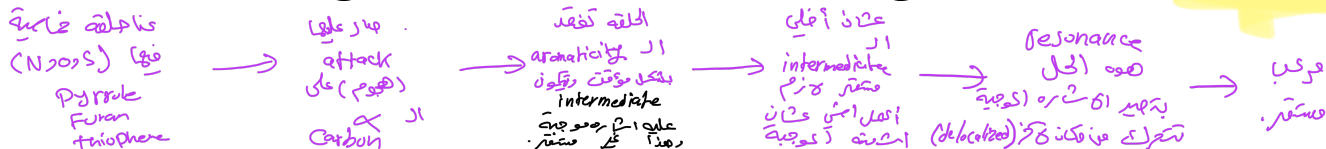
$E^+ \rightarrow \text{electrophile}$



- For all three heterocycles, electrophilic **attack is favored at the alpha carbon of the ring**. An attack at this position leads to an intermediate whose positive charge can be dispersed to all other ring positions; charge dispersal of course is a well-known stabilizing effect. The charge dispersal is shown in Scheme 7.2 with the use of resonance structures.

- Note the critical role of the heteroatom in donating electrons to the ring.

لأنه الهام بالسلامة :



Paal Knorr
Synthesis

← الفانيل ←

Furan

الفانيل



← الفانيل ← Furan ←

1,4-diketone/aldehyde

1,4-diketone

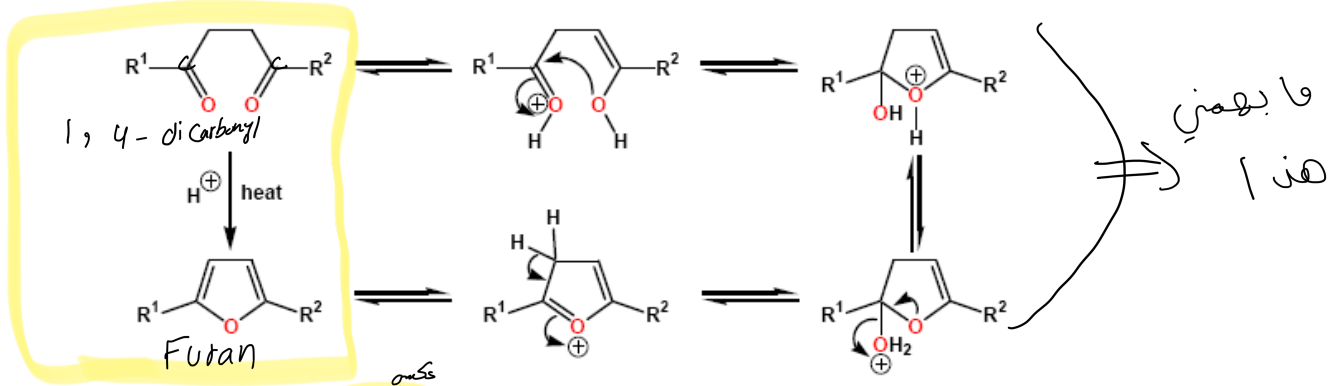
1,4-dialdehyde

1,4-dicarbonyl + H₂O → Furan

H⁺
catalyst

Furans – Synthesis

Paal Knorr Synthesis



- The reaction is usually reversible and can be used to convert furans into 1,4-diketones
- A trace of acid is required – usually TsOH (p-MeC₆H₄SO₃H)

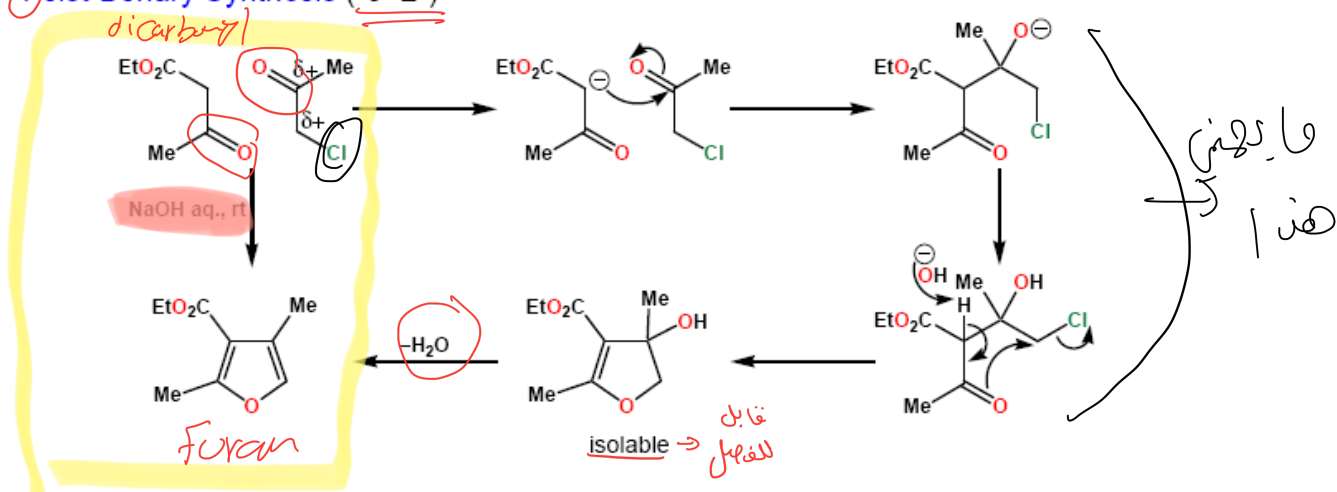
H⁺ (catalyst)

← الفانيل ←
الفانيل

3+2 $\Leftarrow$ cycloaddition between Furan ring
 (Feist-Benary)

فيغ فيغ
 Furan ring

Feist-Benary Synthesis ("3+2")



فان فيغ
 هذا

المركب الناتج
 قبل ازالة H2O
 بنقدر نضاهه بغيره
 معينة

- The product prior to dehydration can be isolated under certain circumstances
- Reaction can be tuned by changing the reaction conditions

مركب فيغ
 Carbonyl group
 دوالة فيغ خارجين

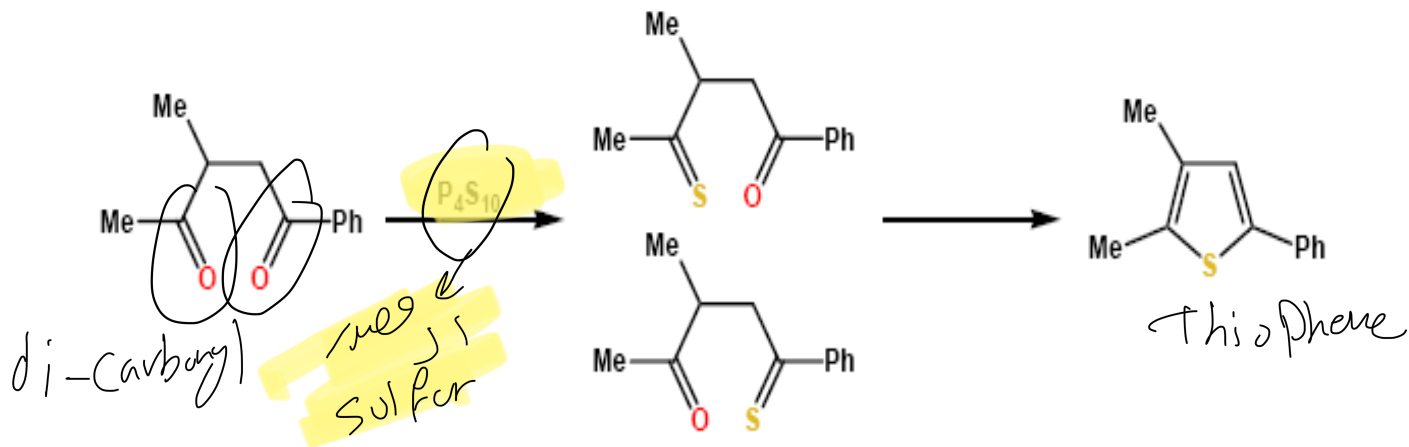
NaOH
 aq.
 rt

Furan

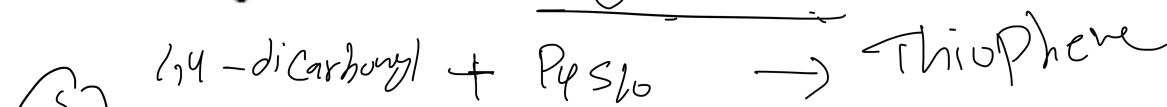


(4+1) ← Paal-Knorr ← Thiophene
 ← S ← Thiophene
Thiophenes – Synthesis
 1,4-dicarbonyl + P₄S₁₀ → Thiophene

Synthesis of Thiophenes by **Paal Knorr** type reaction ("4+1")



• Reaction might occur via the 1,4-bis-thio ketone



(4+1)



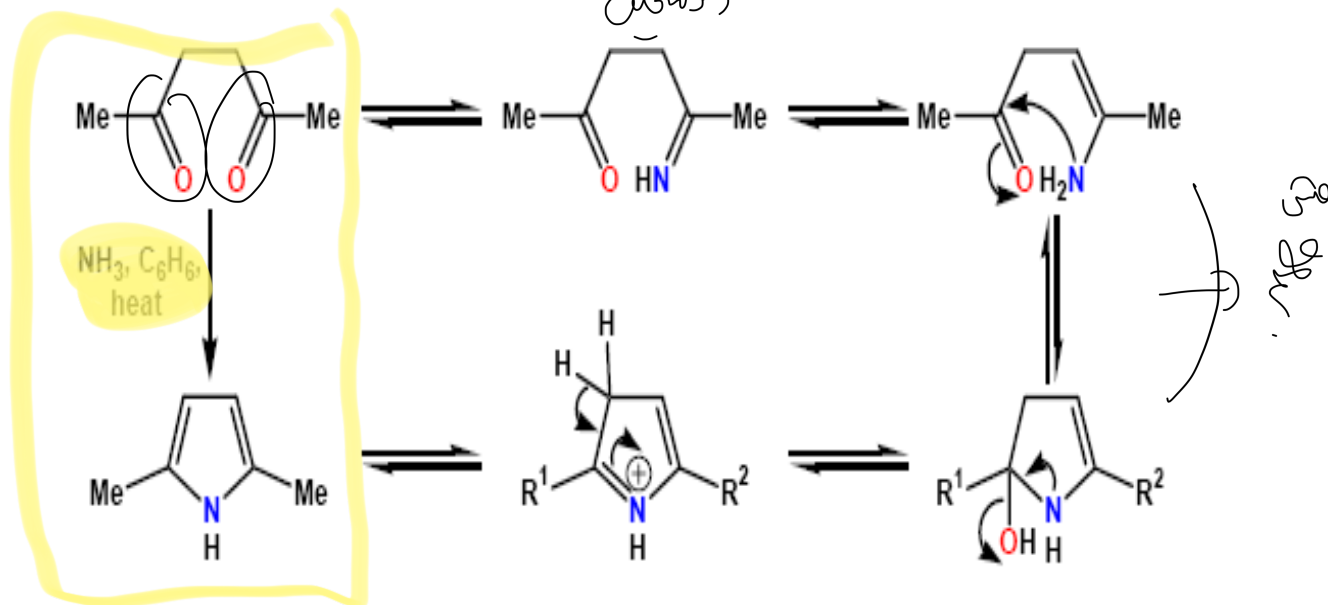
← Paal Knorr ← NH_3 ←
← N لاي ايزولو ← Pyrrole ← المركب

Pyrrole line

Pyrroles – Synthesis

1,4-dicarbonyl + NH_3 → Pyrrole

Paal Knorr Synthesis ("4+1")



- Ammonia or a primary amine can be used to give the pyrrole or N-alkyl pyrrole

NH_3

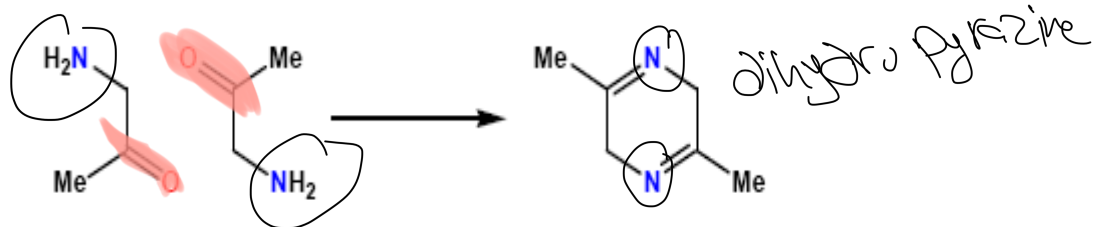
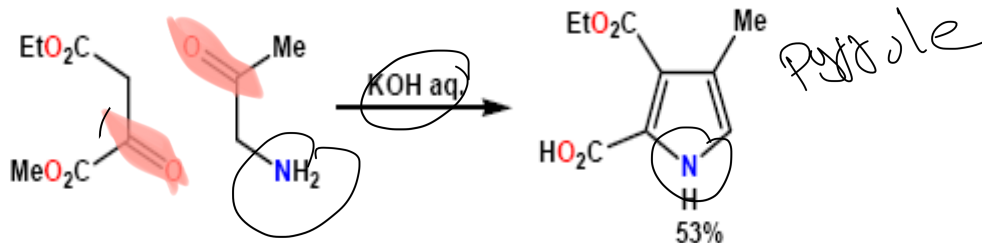
RNH_2

$(3+2) \leftarrow \text{Knorr}$

$\leftarrow \text{cycl-addition w/ 2 pyrrole groups}$

Pyrroles – Synthesis

Knorr Pyrrole Synthesis ("3+2")



• Use of a free amino ketone is problematic – dimerisation gives a dihydropyrazine

$\text{Carbonyl group } \text{C=O}$
 N attached
 $\xrightarrow{\text{KOH}}$ pyrrole
 all group (N)

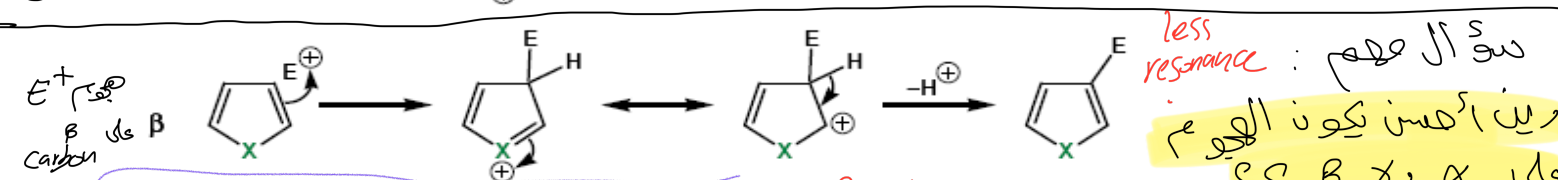
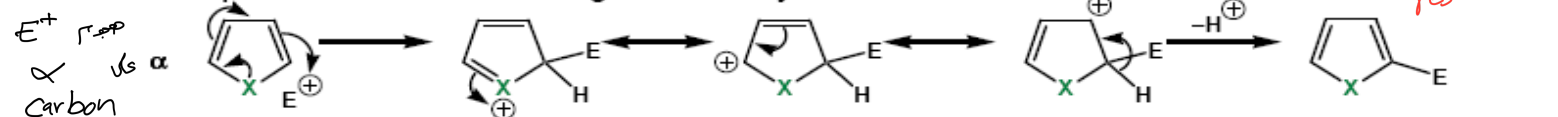
$\text{Free amino ketone} \rightarrow \text{dihydropyrazine}$

↑ resonance

↑ stability

Furans, Pyrroles Thiophenes – Electrophilic Substitution

Electrophilic Substitution – Regioselectivity



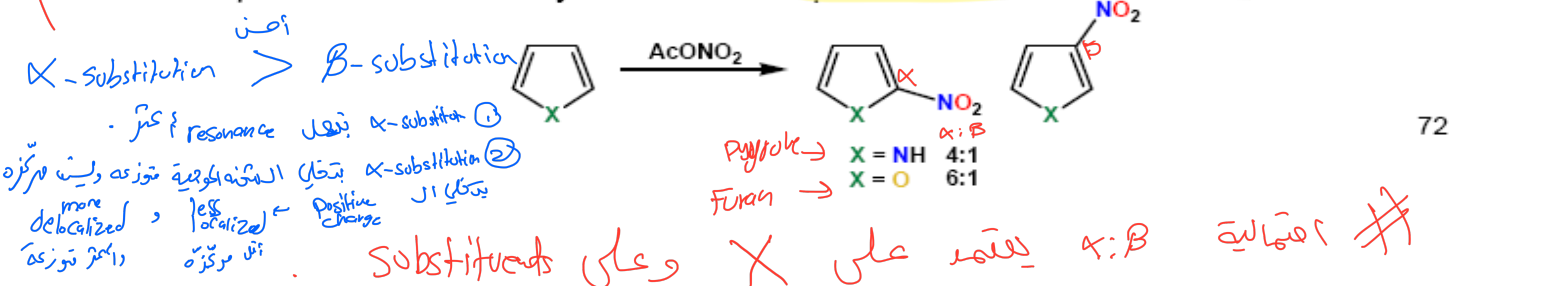
• Pyrrole > furan > thiophene > benzene

• Thiophene is the most aromatic in character and undergoes the slowest reaction

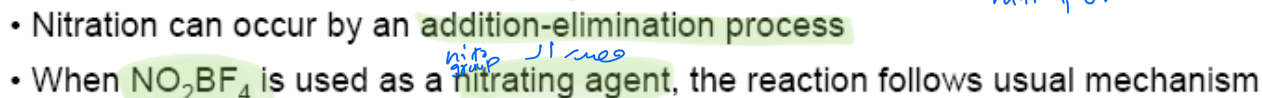
• Pyrrole and furan react under very mild conditions

• α -Substitution **favoured** over β -substitution more resonance forms for intermediate and so the charge is less localised (also applies to the transition state)

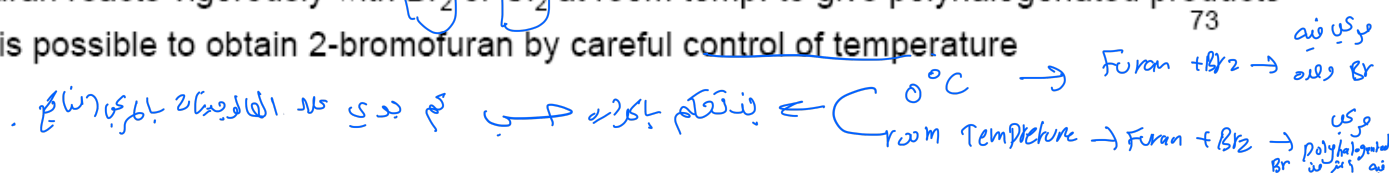
• Some β -substitution usually observed – depends on X and substituents



Nitration of Furans

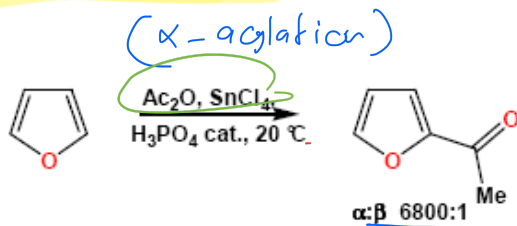


- Furan reacts vigorously with Br_2 or Cl_2 at room temp. to give polyhalogenated products
- It is possible to obtain 2-bromofuran by careful control of temperature

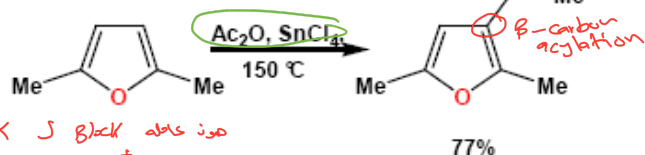


Furans – Electrophilic Substitution

Friedel-Crafts Acylation of Furan



(β -acylation) $\Rightarrow$ لو كملنا block ج α و استخدمنا حرارة عالية.

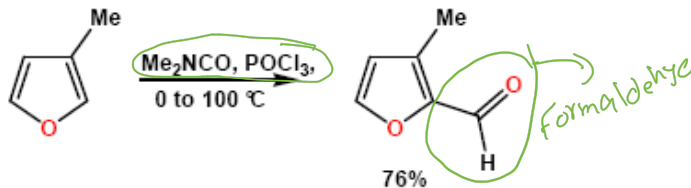


منه كملنا block ج α و استخدمنا حرارة عالية.

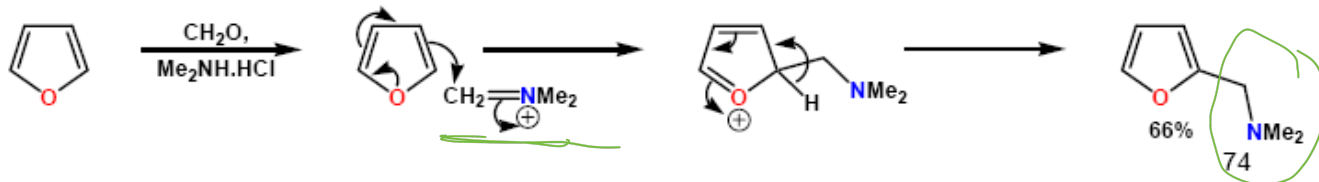
- Blocking groups at the α positions and high temperatures required to give β acylation

Vilsmeier Formylation of Furan

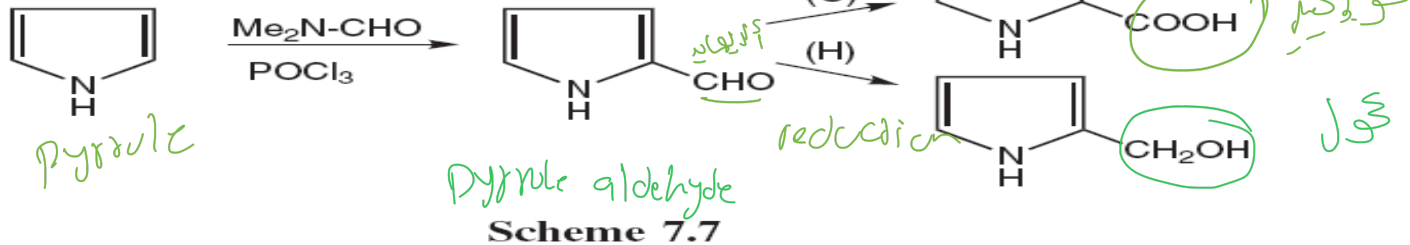
Formaldehyde



Mannich Reaction of Furans

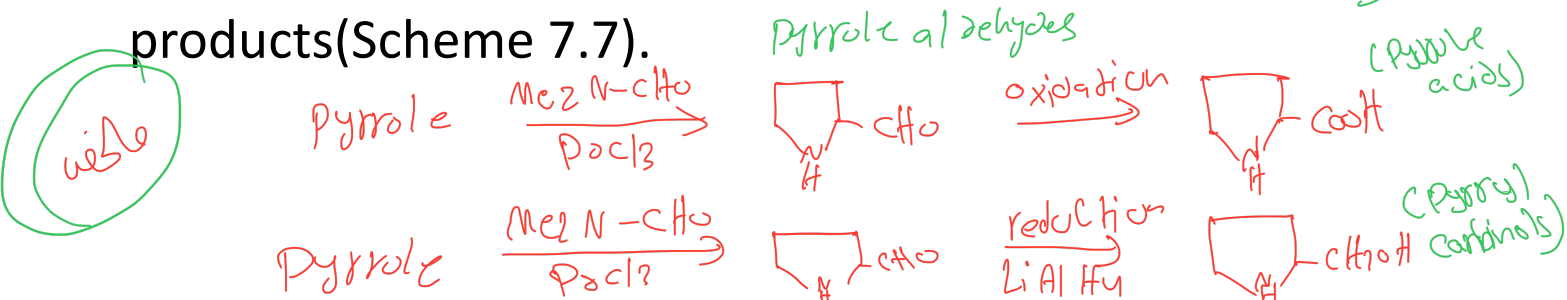


Vilsmeier Formylation of pyrrole:

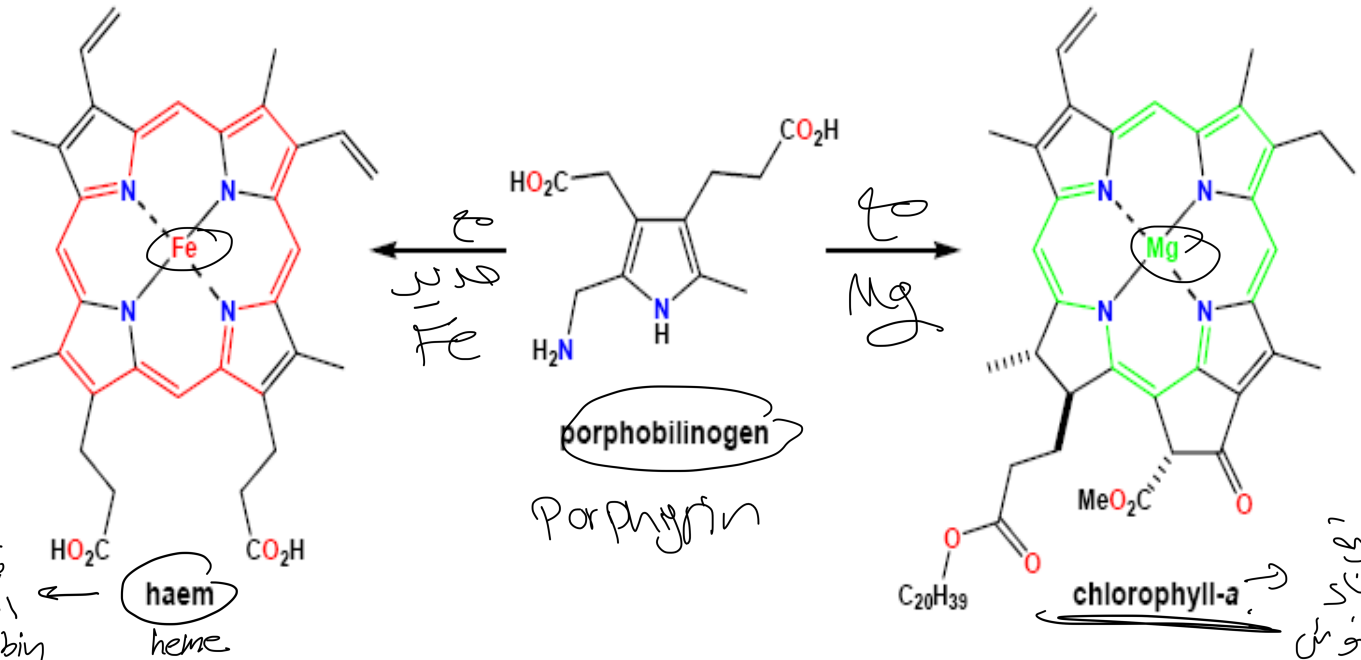


Vilsmeier-Haack Formylation with N,N-Dimethylformamide.

In the presence of phosphorus oxychloride (POCl_3), the —CHO group of N,N-dimethylformamide can be attached to the pyrrole ring (Scheme 7.7). This is a highly useful process for the synthesis of pyrrole aldehydes, which are precursors of pyrrole acids by oxidation, of pyrrol carbinols by reductions with LiAlH_4 , and of other products (Scheme 7.7).



Porphyrin Natural Products



- The pigment haem is found in the oxygen carrier haemoglobin
- Chlorophyll-a is responsible for photosynthesis in plants
- Both haem and chlorophyll-a are synthesised in cells from porphobilinogen.

Basic and Acidic Properties of Pyrroles.

- ***The low electrondensity*** at nitrogen in pyrroles make them weak bases (for pyrrole, K_b about 10^{-17} ; cf. to noncyclic amines at about 10^{-5}),
- *it is not* possible to make salts of pyrroles with aqueous acids.
- In fact, as will be shown next, **protonation takes place on carbon, not on nitrogen.**
- pyrroles **do not form quaternary salts** with alkylating agents, or amine oxides with peroxy compounds.
- This is in stark contrast with pyridines.
- Another explanation for the unavailability of the electron pair on nitrogen in pyrroles is that the aromatic sextet (and its energy of stabilization) would be destroyed if it were used in forming a bond.

السكريد يلي قبل سو بيحي:

Pyrrrole



اثنين يعبروا

weak
Bases

Pyridine



① lone pair of e^- ← بورعوا على ال Ring

ديالائي بطال قوفين كذي
low electrophilicity ← (Unavailable electrons)

② قابقدر يتبين proton لاني

production كذي protonation على ال N
مردود كربون

quaternary salts ③ قابقدر ليكوي كذي

alkylating agent
وفي حالة كذا + acid
مارد تامين ال N
amine oxides
with Peroxy Compounds.

① lone pair of e^- ← يال ال ring

(available electrons)

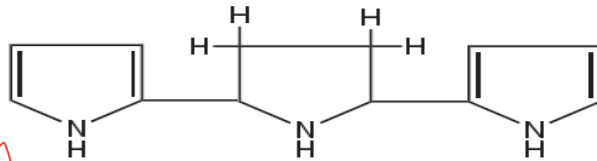
معا لقم قوفين

high density of e^-

② بصر كذي protonation على ال N

③ quaternary salts

N ۲۳ تہا
C ۲۳ تہا



عز
حید

Pyrrole $\xrightarrow[\text{heat}]{\text{strong acid}}$ Polymer (Undesirable)

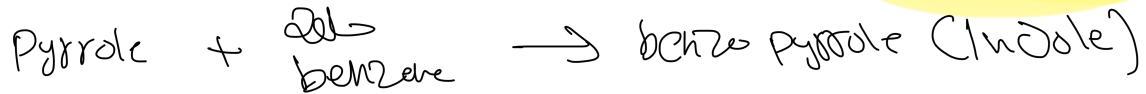
- When pyrrole is heated with strong acids, a crystalline compound is
- formed that contains three pyrrole units. Its structure has been established as **7.4. Strong acids can also cause the undesirable formation**

of polymeric products from pyrrole.

These processes depend on the protonation of carbon of the ring, not of nitrogen.

دائماً ہوا ہے کہ pyrrole acidic media میں ہائیڈروجن کی پروٹونیشن کا اثر
پیر کے اے ویکوٹن مرکب (Polymer) کے عر حید

Benzo Derivatives of Pyrroles (Indoles)

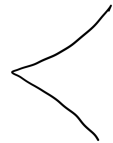


- The indole family is one of the most important of all heterocyclic families, and the chemistry of this system is vast.
- Many natural products and synthetic medicinals contain this nucleus.
- Electrophilic substitutions occur readily with an attack on the electron-rich pyrrole moiety rather than the benzene ring. The 3-position is entered in preference to the 2-position, but if the 3-position is blocked, substitution occurs at the 2-position,

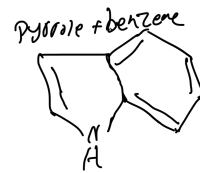
جزيئات طبيعية أو صناعية CNS

البنزين أكثر غنى إلكترونيًا من البيرول
لذلك فإن البيرول هو الموقع المفضل لمعظم التفاعلات
التي تحدث في البيرول (مثل التفاعلات الكهروضوئية)
وإذا كان الموقع 3 محظورًا، فإن التفاعل يحدث في الموقع 2.

Pyrrole



Indole



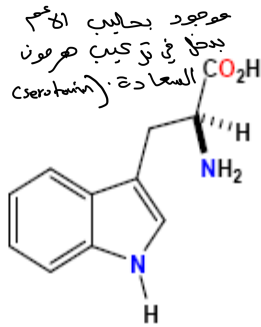
more electron Rich.
وبالتالي فإن البيرول هو الموقع المفضل لمعظم التفاعلات
التي تحدث في البيرول (مثل التفاعلات الكهروضوئية)
وإذا كان الموقع 3 محظورًا، فإن التفاعل يحدث في الموقع 2.

الموقع

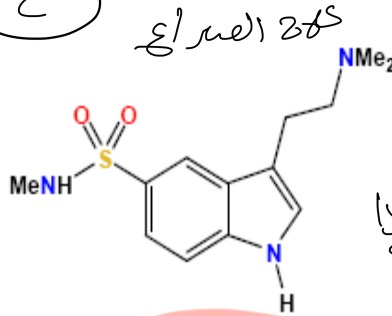
هذه أمثلة من Indole group

Indoles – Bioactive Indoles

هذا المصنوع
يجعل ادمان
يجعل تفتير
الدماغ

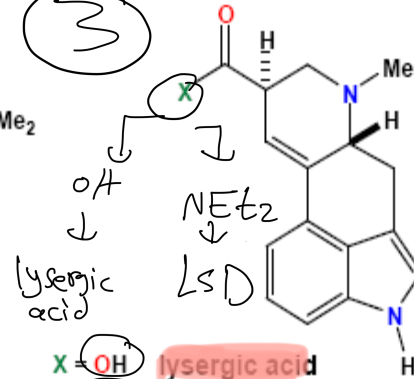


tryptophan



sumatriptan

يؤخذ هذا في



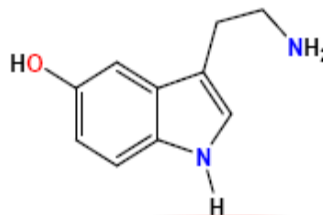
X = OH
X = NEt₂

lysergic acid

lysergic acid diethylamide (LSD)

- Tryptophan is one of the essential amino acids and a constituent of most proteins
- Sumatriptan (Imigran®, GSK) is a drug used to treat migraine and works as an agonist for 5-HT receptors for in the CNS
- LSD is a potent psychoactive compound which is prepared from lysergic acid, an alkaloid natural product of the ergot fungus

decarboxylation
أزالة COOH



5-hydroxytryptamine (serotonin)

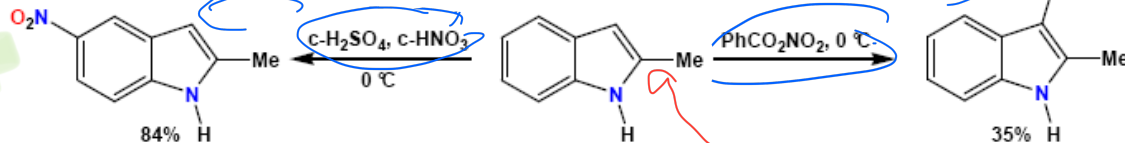
هرمون المعادلة

يقلع
in CNS

خلاصة
يلاحظ انه كل هاء (الترقية)
لله فاعل: هاء في Indole
في نية barer وهو hydrophilic
يقلع على الدخول لل
barrier . Brain

Indoles – Electrophilic Substitution

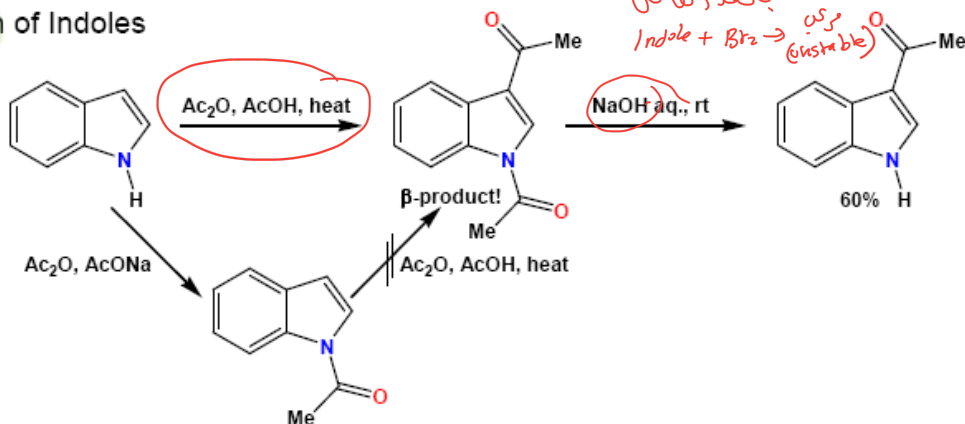
Nitration of Indoles



- Polymerisation occurs when there is no substituent at the 2-position
- Halogenation is possible, but the products tend to be unstable

لوعاى 2-position
فا حتى ده بيسر خراب
polymerization

Acylation of Indoles

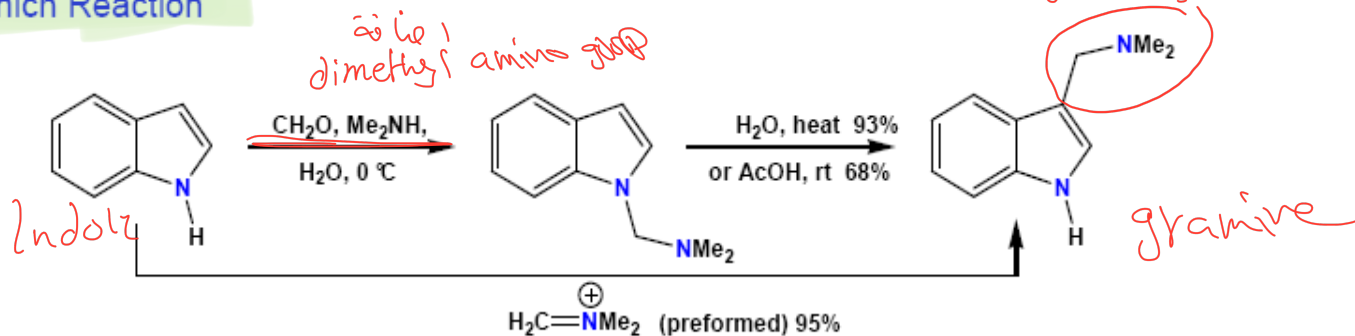


- Acylation occurs at C before N because the N-acylated product does not react

acylation
(اول امتي على الكربون
بعدين على ال N)

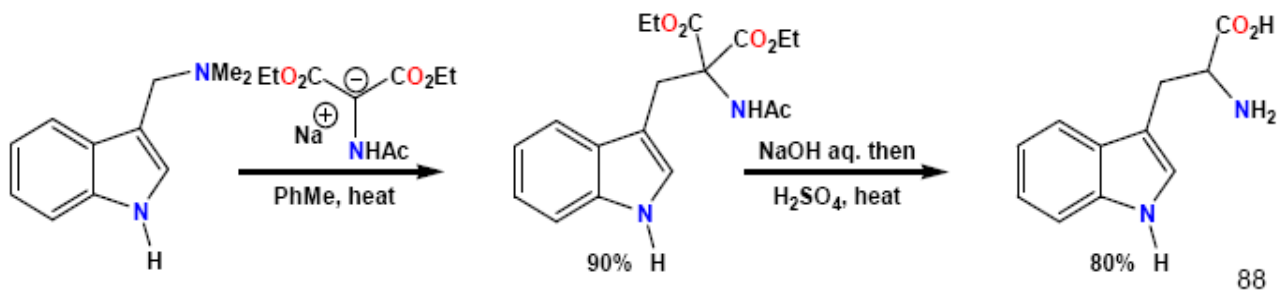
Indoles – Electrophilic Substitution

Mannich Reaction



- A very useful reaction for the synthesis of 3-substituted indoles
- The product (gramine) can be used to access a variety of other 3-substituted indoles

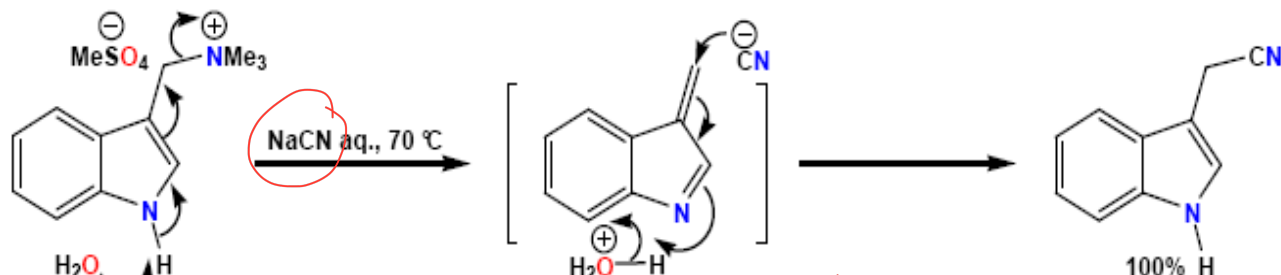
Synthesis of Tryptophan from Gramine



gramine $\longrightarrow$ Tryptophan

Indoles – Electrophilic Substitution

Synthesis of Other 3-Substituted Indoles from Gramine

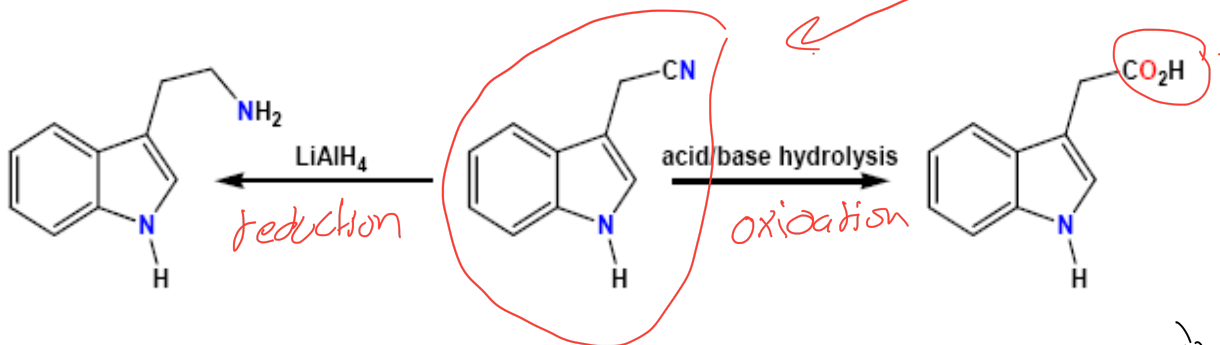


gramine

dimethylamine NMe_2
(CN) cyano group added

3-substituted indole

- The nitrile group can be modified to give other useful functionality



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