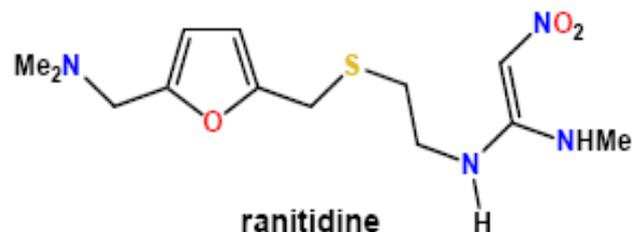


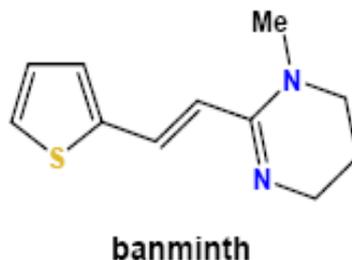
PI-EXCESSIVE RING SYSTEMS



- Ranitidine (Zantac®, GSK) is one of the biggest selling drugs in history. It is an H₂-receptor antagonist and lowers stomach acid levels – used to treat stomach ulcers



- Ketorolac (Toradol®, Roche) is an analgesic and anti-inflammatory drug

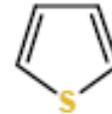
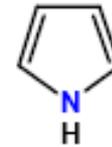
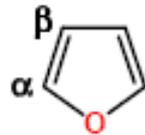


- Pyrantel (Banminth®, Phibro) is an anthelmintic agent and is used to treat worms in livestock

Furans, Pyrroles and Thiophenes – Structure

حلقه حناسته

Structure

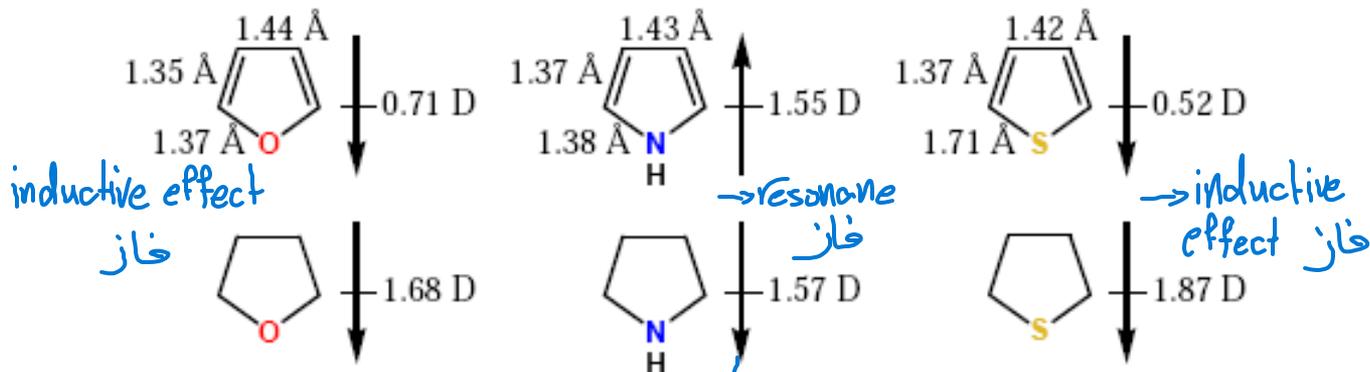


- 6 π electrons, planar, aromatic, isoelectronic with cyclopentadienyl anion

Resonance Structures



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



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

PI excessive عشان هيك عا هون

Chemical Properties of Pyrroles

Electrophilic Substitution.

A significant feature of the pi excessive

- ring systems is that they are highly reactive to electrophilic → because rich in electron

species, totally unlike the pi-deficient rings. → poor electron

← انتكات الحلقات
الاي
أخذناهم
حرف

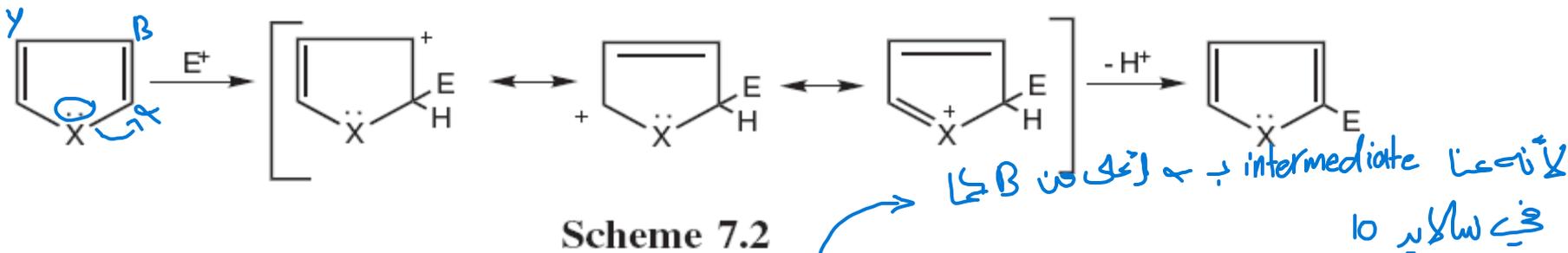
The reactivity is greater than that of benzene and is in roughly the same range as found for benzenes bearing electron releasing groups as in aniline. مشتقات البنزين

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

- pyrrole > furan > thiophene > benzene

↳ resonance dominate

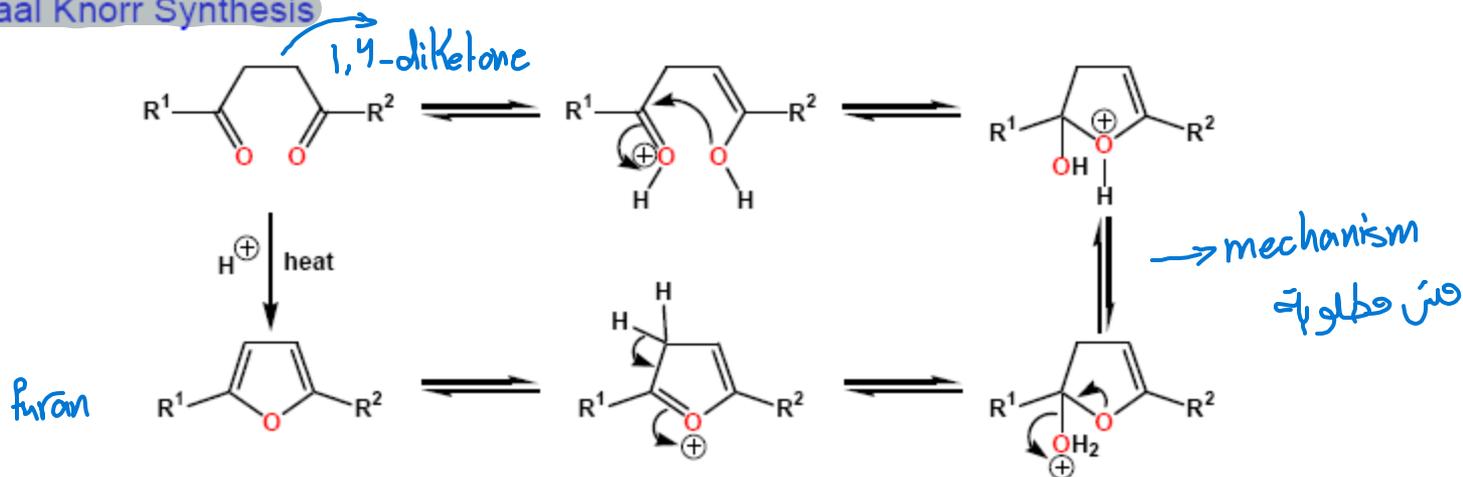


- For all three heterocycles, **electrophilic attack is favored at the alpha carbon** of the ring. An attack at this position leads to an **intermediate whose positive charge can be dispersed to all other ring positions**; charge dispersal of course is a well-known **stabilizing effect**. The charge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

(heteroatom) بشارك الإلكترونات تبعونها بالحلقة سواء كان negative inductive حسيبر لو لم يكن

Furans – Synthesis

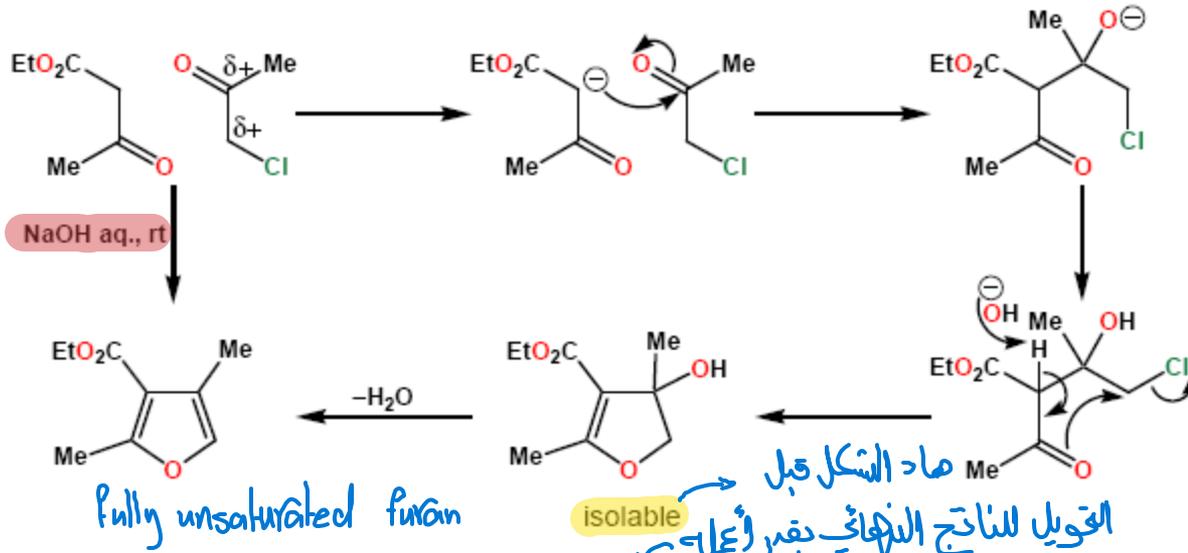
Paal Knorr Synthesis



- The reaction is usually reversible and can be used to convert furans into 1,4-diketones
- A trace of acid is required – usually TsOH ($p\text{-MeC}_6\text{H}_4\text{SO}_3\text{H}$)

Feist-Benary Synthesis ("3+2")

condition التي عنا هون
basic condition



صاـد الشكل قبل
القول للناجـة النهائي بغير العمل

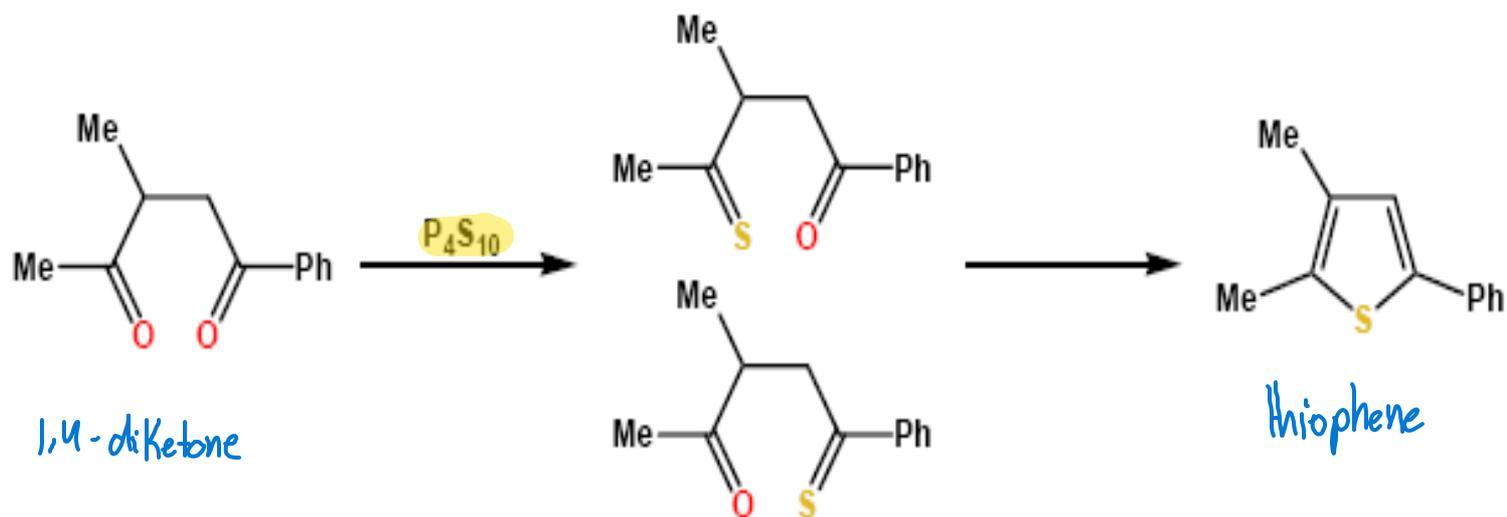
- The product prior to dehydration can be **isolated** under certain circumstances
- Reaction can be **tuned by** changing the reaction conditions

شروط

لنم ضبطها لروالكم
فبها عن طريق

Thiophenes – Synthesis

Synthesis of Thiophenes by Paal Knorr type reaction (“4+1”)

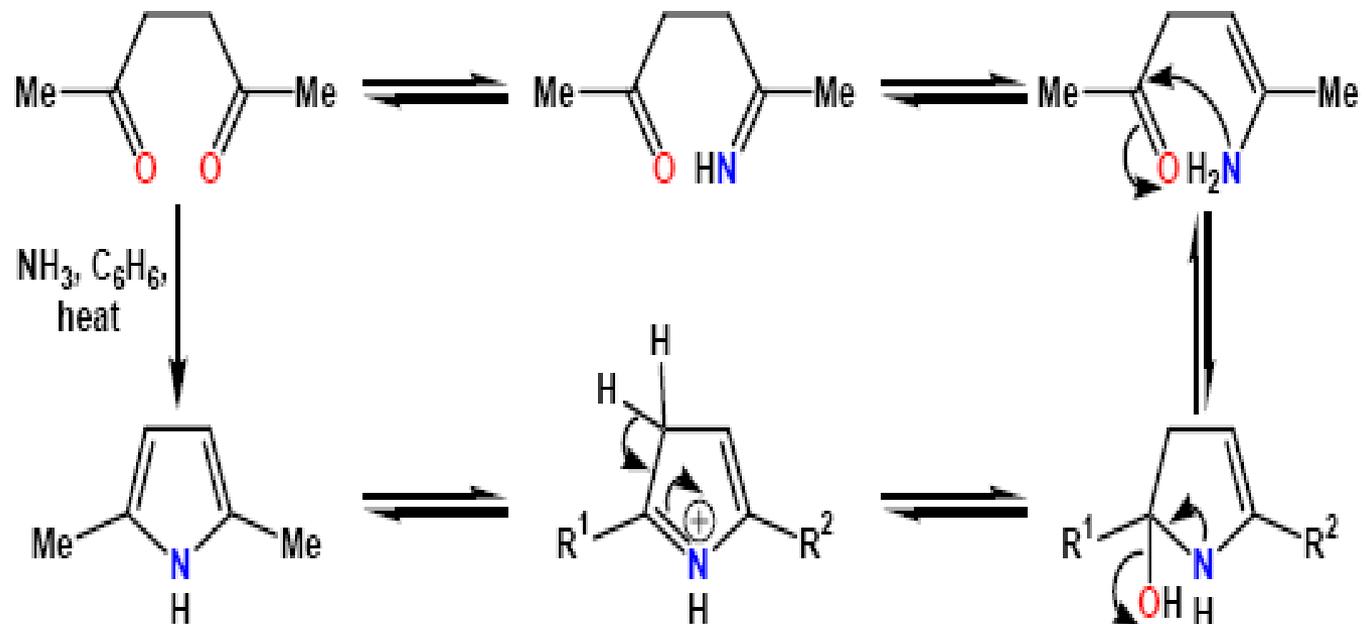


- Reaction might occur via the 1,4-bis-thio-ketone

بجوں کے متبادل لانا ج thiophene

Pyrroles – Synthesis

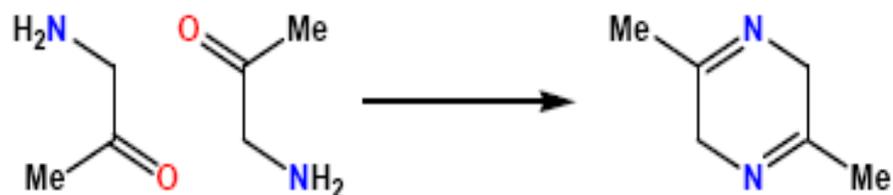
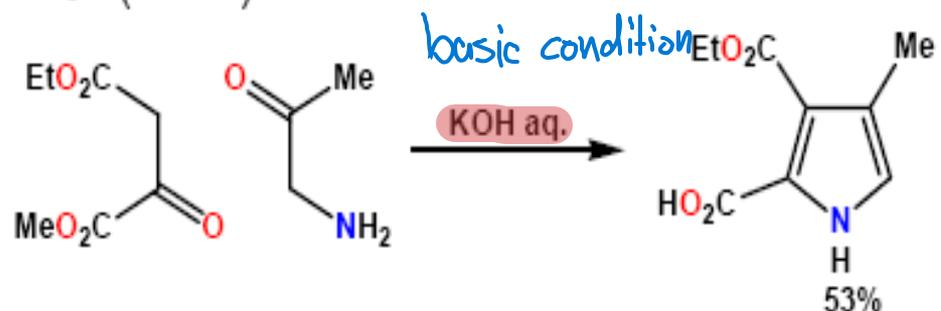
Paal Knorr Synthesis ("4+1")



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

Pyrroles – Synthesis

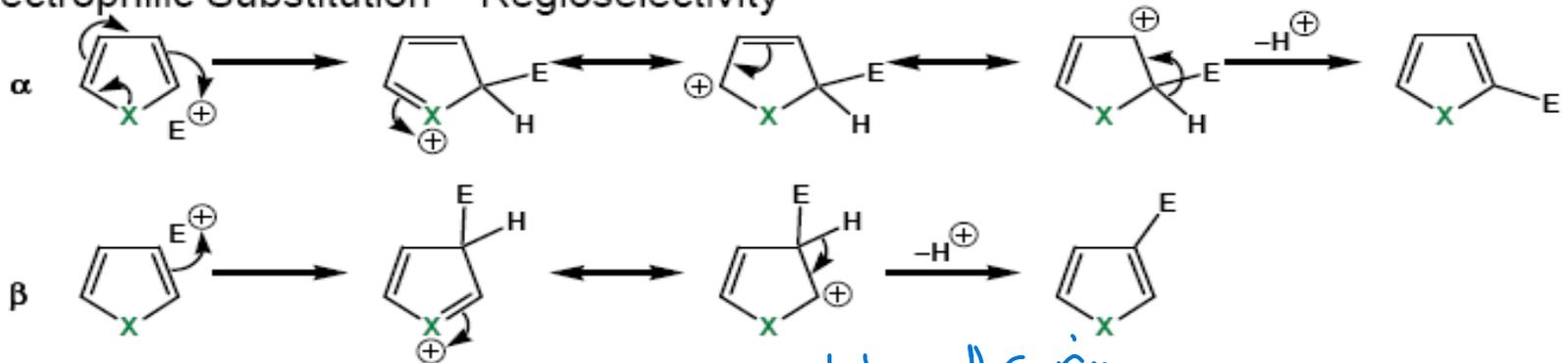
Knorr Pyrrole Synthesis ("3+2")



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

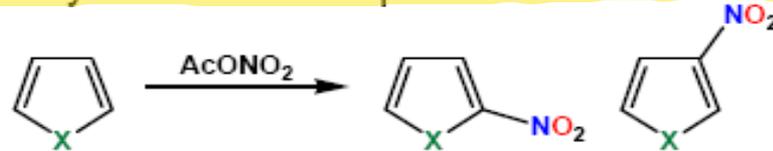
Furans, Pyrroles Thiophenes – Electrophilic Substitution

Electrophilic Substitution – Regioselectivity



- Pyrrole > furan > thiophene > benzene *↔ between three ring*
- Thiophene is the most aromatic in character and undergoes the slowest reaction
- Pyrrole and furan react under very mild conditions *يعني ظروف بسيطة*
- α -Substitution favoured over β -substitution *why?* 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

يعني ما يتطل بمكان واحد



X = NH 4:1
X = O 6:1

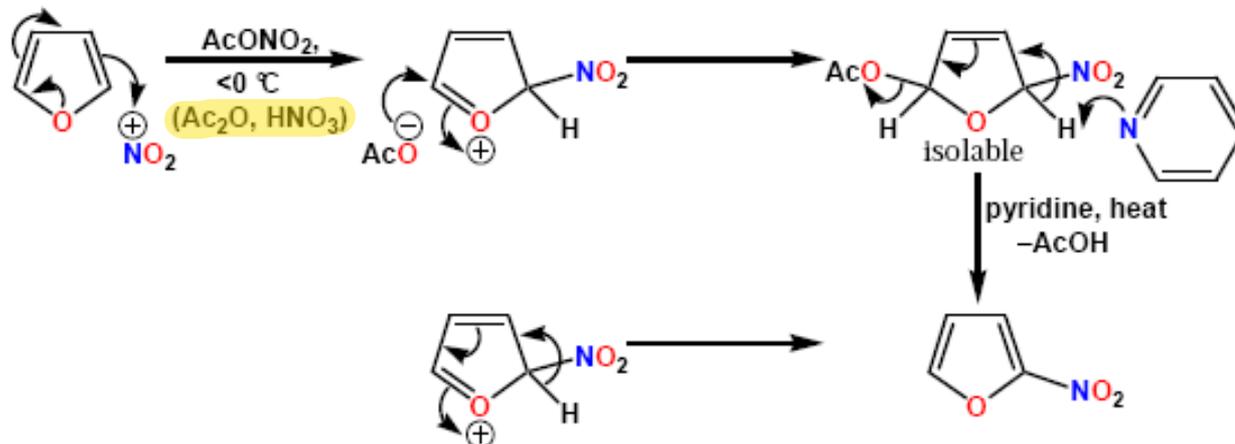
هذا كل خمس جزئيات يتم الاستبدال في موقع α اربع مرات والموقع بيتأخر واحدة

لست مرات α مرة B

التوضيح

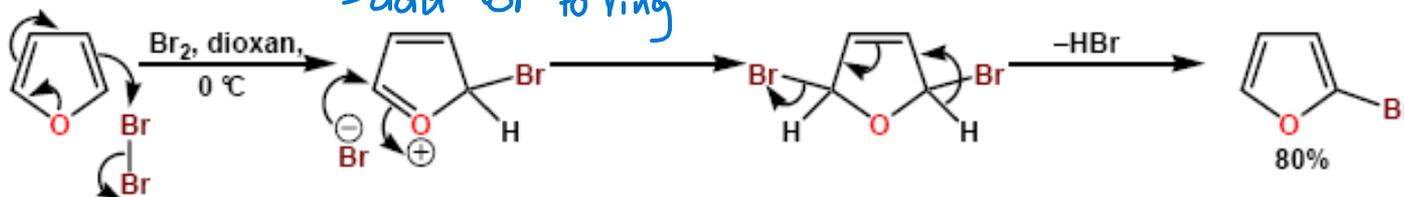
Furans – Electrophilic Substitution

Nitration of Furans → add NO₂ to furan



- Nitration can occur by an addition-elimination process
- When NO₂BF₄ is used as a nitrating agent, the reaction follows usual mechanism

Bromination of Furans

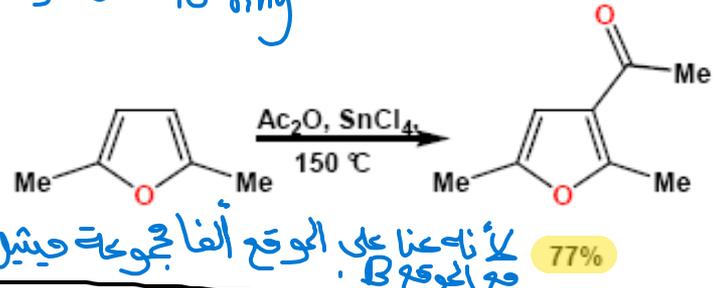
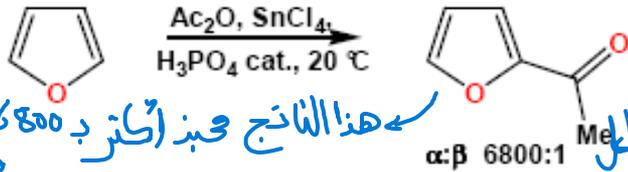


- Furan reacts vigorously with Br₂ or Cl₂ at room temp. to give polyhalogenated products
- It is possible to obtain 2-bromofuran by careful control of temperature → zero C°

في اذا بدنا نتحكم بعدد ذرات البرون على الحلقة يجب التحكم بدرجة الحرارة

Furans – Electrophilic Substitution

Friedel-Crafts Acylation of Furan → add $\text{CH}_3-\overset{\text{O}}{\parallel}{\text{C}}^+$ to ring

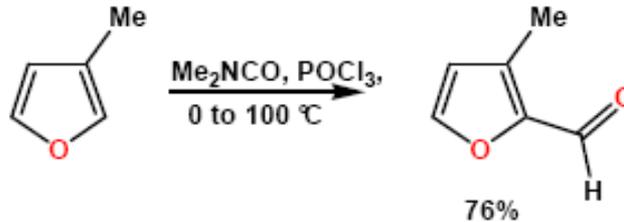


هذا الناتج جيد أكثر بـ 6800 مرة على الموقع α من الموقع β .

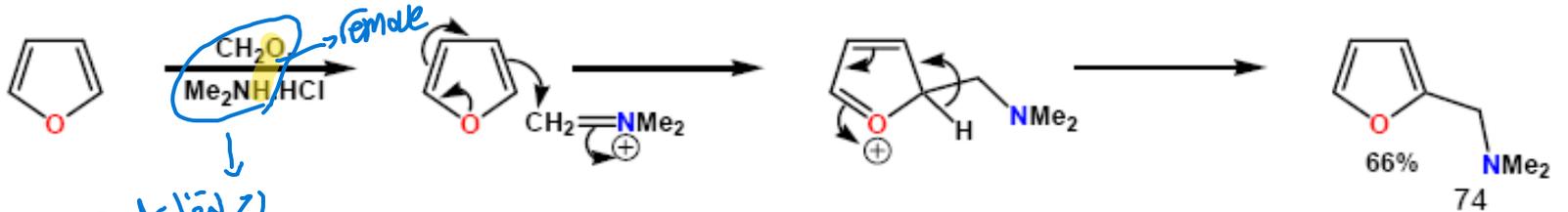
لأننا هنا على الموقع ألفا مجموعة ميثيل تحجب الموقع β .

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

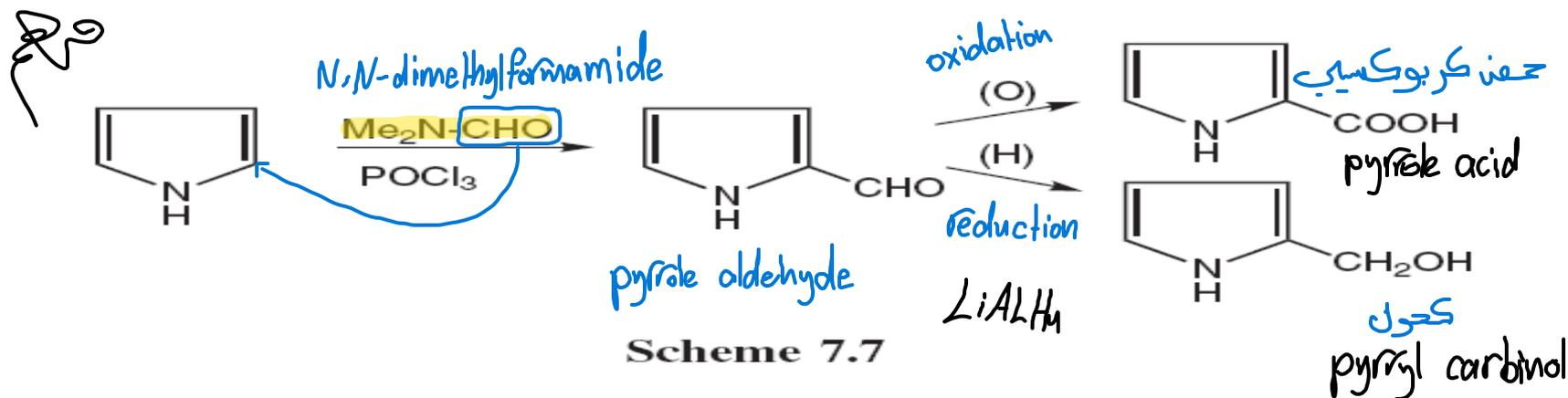
Vilsmeier Formylation of Furan



Mannich Reaction of Furans



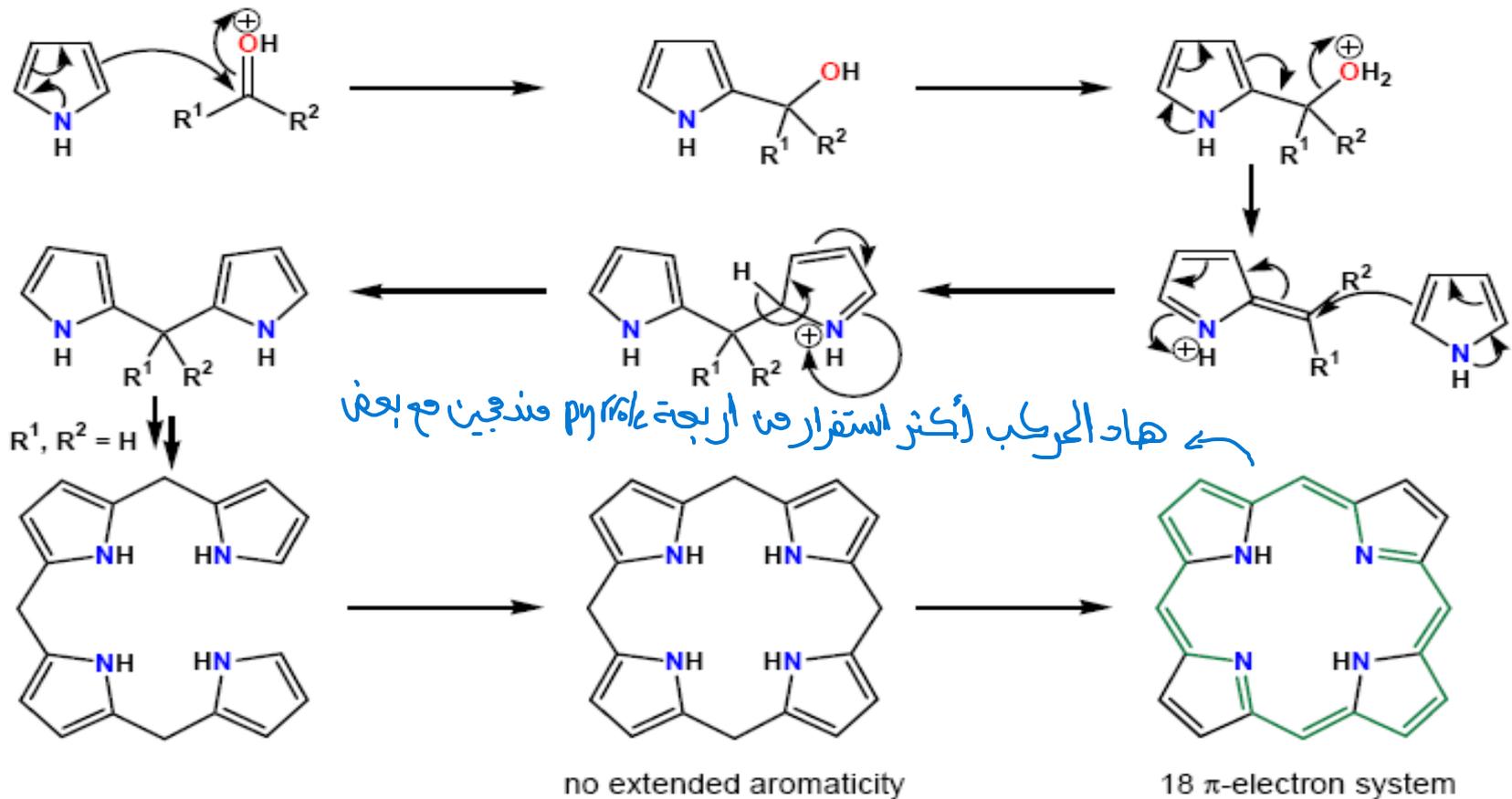
يحيد ويتفاعل مع بعض ring = $\text{CH}_2\text{Me}_2\text{N}$



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).

Pyrroles – Porphyrin Formation

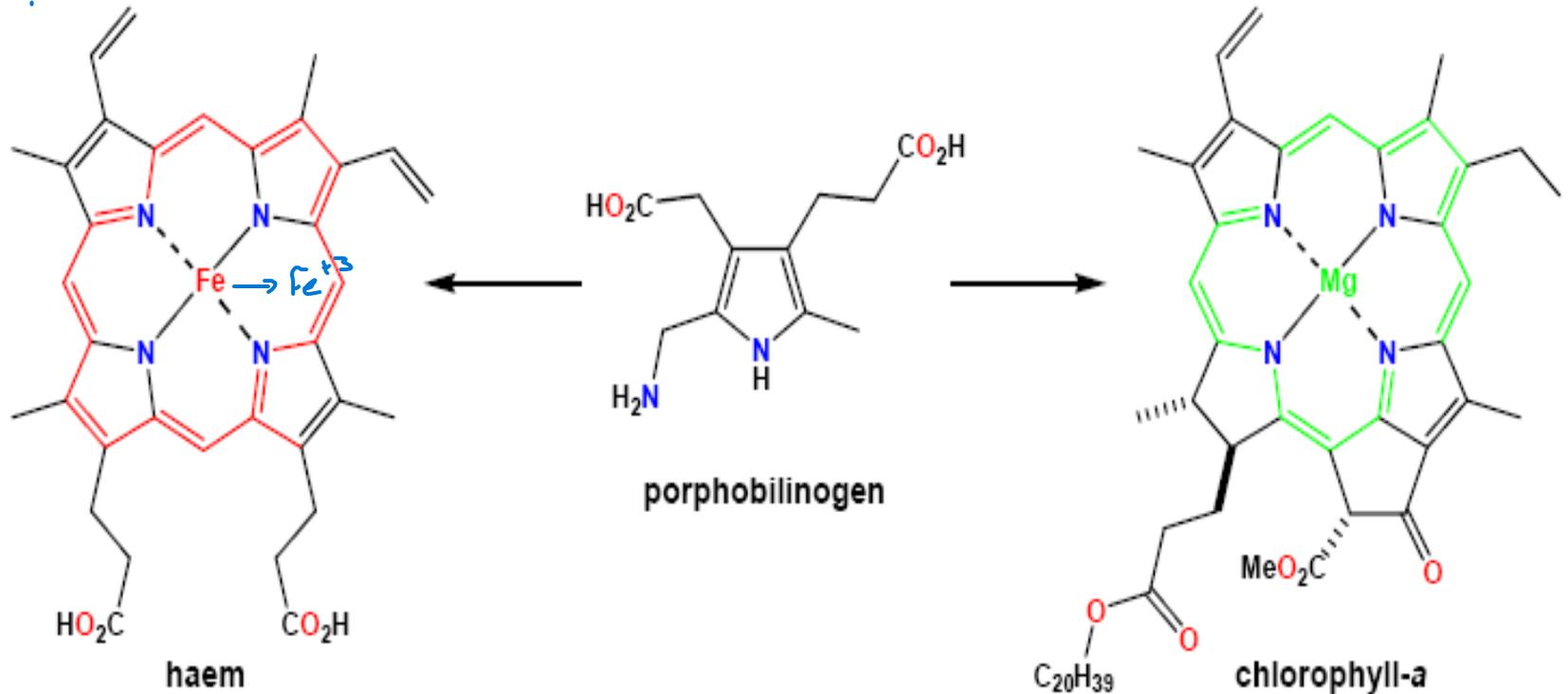


هذا المركب أكثر استقراراً من أربعة pyrrole منفجين مع بعض

- The extended aromatic 18 π -electron system is more stable than that having four isolated aromatic pyrroles

Porphyrin Natural Products

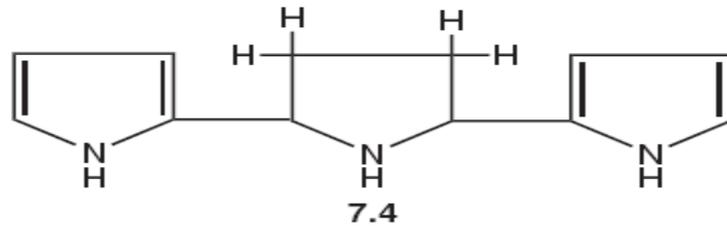
التفاعل اجاب بالسنوات



- 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 electron density** 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. ← لأنه قاعدة ضعيفة
 - 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.** ①
 - This is in **stark contrast with pyridines.** حالة سداسية مرتبطة بـ N
 - 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. تفاعل هذا الزوج من الإلكترونات سيهدم الشكل السداسي العطري (aromatic sextet) ← تدبير الاستقرار للحلقة
- لأنه الإلكترون يدخل resonance كلفة اليون لو
عائودني إلى تدبير الحلقة.



- 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

غير مرغوب فيها

of polymeric products from pyrrole.

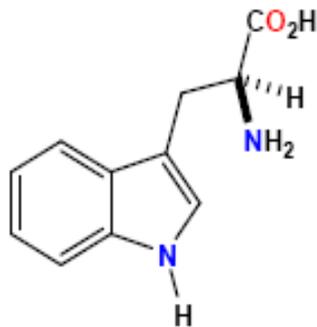
These processes depend on the protonation of carbon of the ring, not of nitrogen.

Benzo Derivatives of Pyrroles (Indoles)

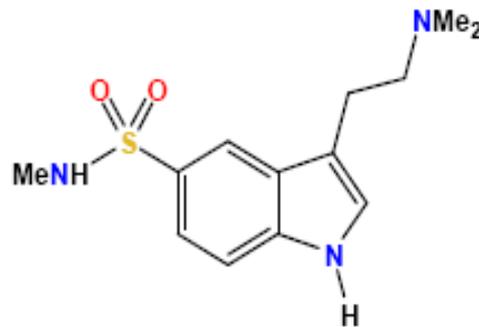
← عبارة عن بيرول وبنزين

- The indole family is one of the most important of all heterocyclic families, and the chemistry of this system is vast. واسعة جدًا
- Many natural products and synthetic medicinals contain this nucleus. تحتوي على الإنزول كنواة لها
- 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, يعني يشبه الحوقع بيتا

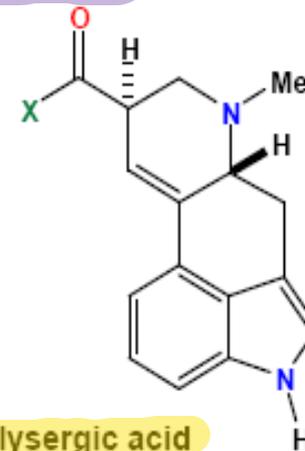
Indoles – Bioactive Indoles



tryptophan



sumatriptan



X = OH lysergic acid
X = NEt₂ 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



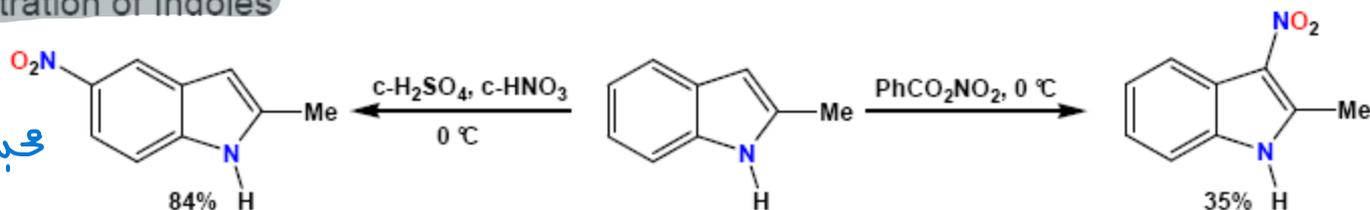
5-hydroxytryptamine (serotonin)

← آتج تفاعل بصير على
pyrrole.

Indoles – Electrophilic Substitution

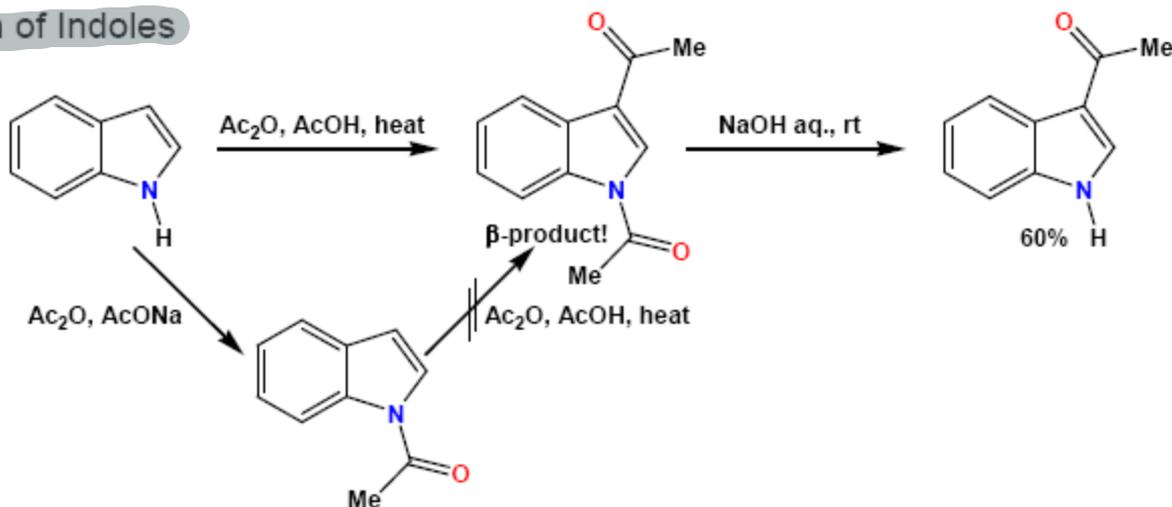
Nitration of Indoles

← هون التفاعل
عبدال بصير على حلقة
البزيت



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

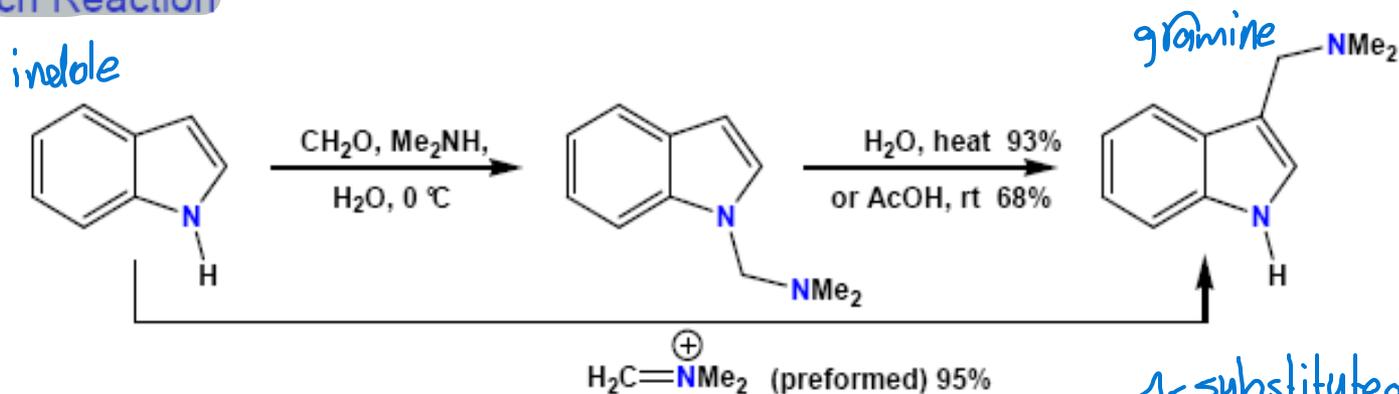
Acylation of Indoles



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

Indoles – Electrophilic Substitution

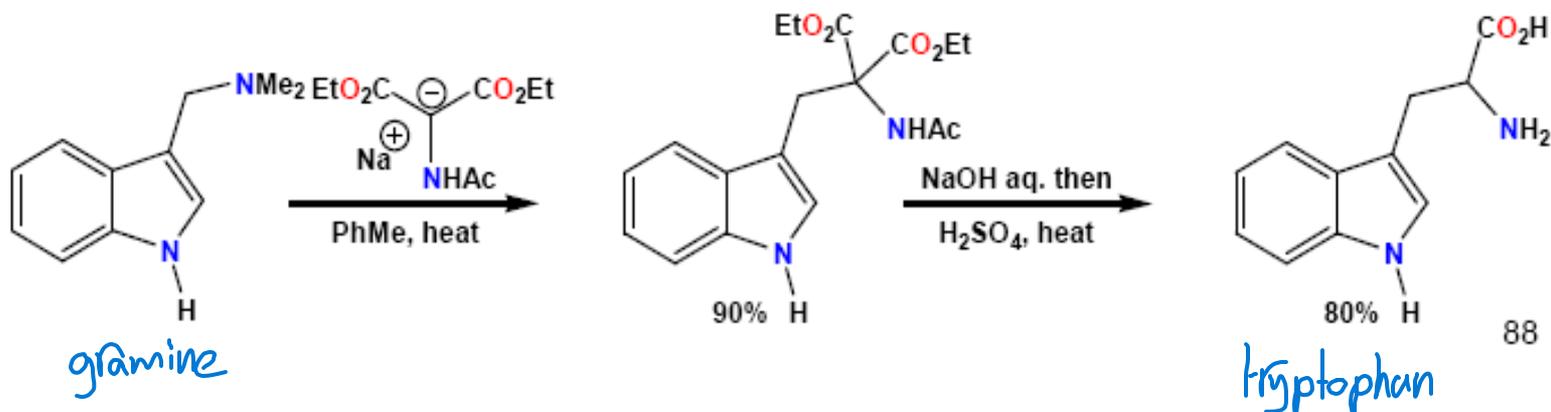
Mannich Reaction



- 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

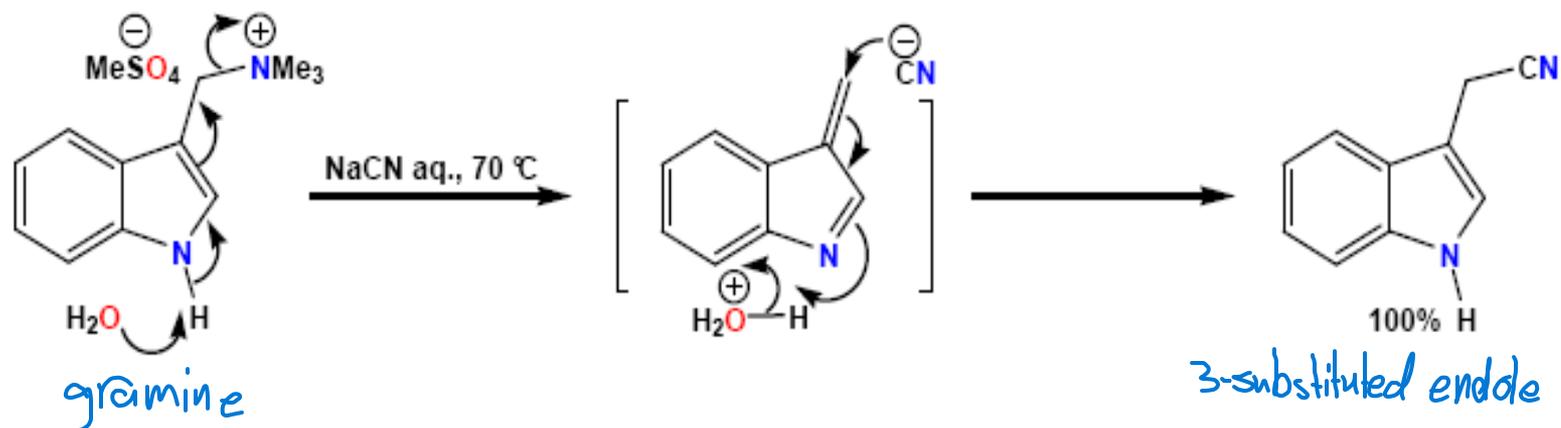
تصنيف substituted على موقع ثلاث

Synthesis of Tryptophan from Gramine



Indoles – Electrophilic Substitution

Synthesis of Other 3-Substituted Indoles from Gramine



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

