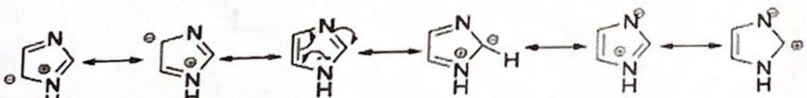
Introduction to Imidazole

Imidazole is a planar, 5-membered heterocyclic ring containing 2 nitrogen atoms at the 1- and 3-positions. The two nitrogen atoms have differing reactivities: one like pyridine and the other like pyrrole. Imidazole is a highly polar, water-soluble compound

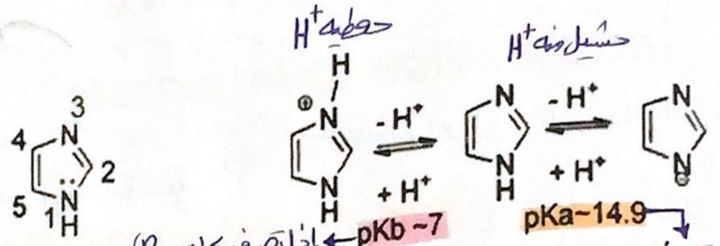
Imidazole is classified as an aromatic compound with 6π electrons and has aresonance energy of ~ 50 kJ/mol. The resonance energy of imidazole is lower than benzene



Resonance Structures of Imidazole

- Imidazole is an amphoteric molecule, acting as both an acid and a base. As an acid, it has a pKa of about 14.9, making it less acidic than
- carboxylic acids or phenol but more acidic than alcohols. As a base, imidazole has a pKb *of about 7, making imidazole much more basic than* pyridine

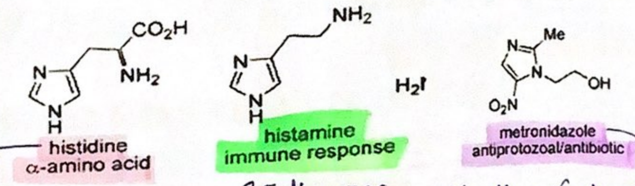
H⁺ حوطنه   H⁺ حشيل منه



Tow Double Bond فيه ← Imidazole (Base) إذا تصرف كـ ← pKb ~7   pKa~14.9 → إذا تصرف كـ (acid)

Imidazole Numbering and pKa's

- The imidazole molecule is incorporated into many biologically relevant molecules.
- several medicines or potential medicines have been made that contain imidazole.



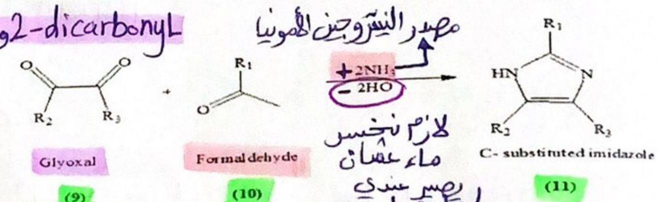
Carboxylic acid بشيل منه ← histidine
histamine فبيعطيني

موجود بال GI & Brain....

دواء مشهور بالصيدليات

قاعدة: أي دواء عبارة عن حلقة aromatic راكب عليها NO2 (nitro group) ← It's not safe. خصوصاً للأطفال

1,2-dicarbonyL   مصدر النيتروجين الأمونيا

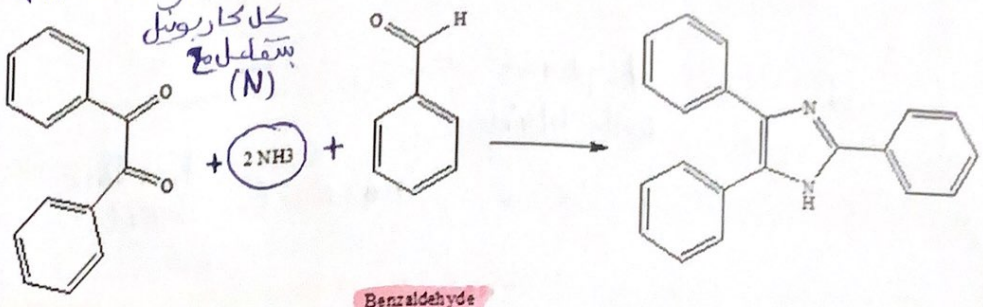


* سلبية هذه الطريقة إنه بنخسر كثير من وزن ال Product

لازم نخسر ماء عشان يصير عندي unsaturated system

- **1) Debus Synthesis:-**
  Debus Synthesised imidazole by using glyoxal **(9)** and formaldehyde **(10)** in ammonia. This synthesis, while producing relatively low yields, is still used for creating C-substituted imidazoles **(11)**. [17]

- **2) Radiszewski Synthesis:**
  Radiszewski reported the condensation of a dicarbonyl compound, benzil **(12)** and a- ketoaldehyde, benzaldehyde **(13)** or a-diketones in the presence of ammonia, yield 2, 4, 5-triphenylimidazole **(14)**. [18]

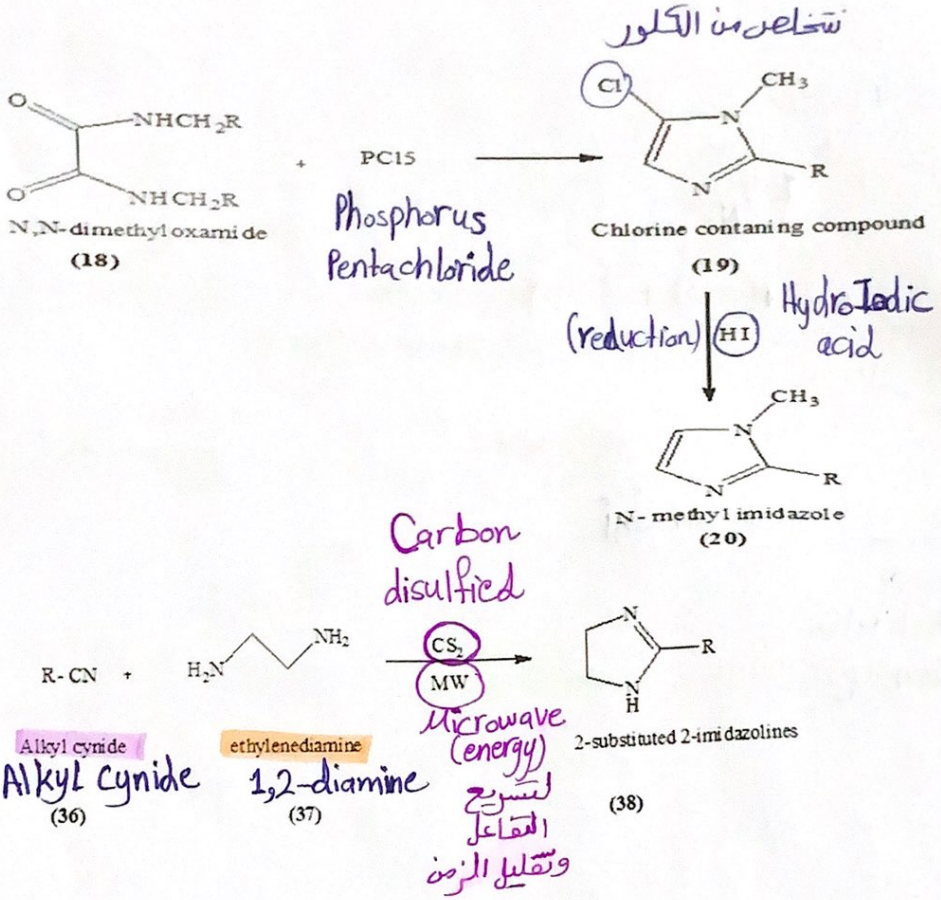


Benzil
(12)

Benzaldehyde
(13)

2,4,5 - triphenylimidazole
(14)

- **Wallach Synthesis:-**
  Wallach reported that when N, N-dimethyloxamide **(18)** is treated with phosphorus pentachloride, a chlorine containing compound **(19)** is obtained which on reduction with hydroiodic acid give N-methyl imidazole **(20)**. Under the same condition N, N-diethyloxamide is converted to a chlorine compound, which on reduction gives 1- ethyl –2- methyl imidazole. [20]
- Pathan *et al* [27] reported the reaction of alkyl cyanide **(36)** with ethylene diamine **(37)** in the presence of carbon disulphide give 2-substituted 2-imidazolines **(38)** under microwave irradiation. The yields of product obtained using this protocol is significantly high and the reaction time is reduced.



Reactivity of the Imidazole Ring

- *Nitrogen A lkylation*
- Alkylation of the nitrogen occurs readily and is either via direct SN2 or SN2', depending on the basicity of the reaction mixture and the electrophile. Sterics of the N-alkylating group with other substituents will also play a role.

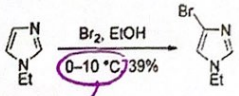
1Step

PH حسب ال

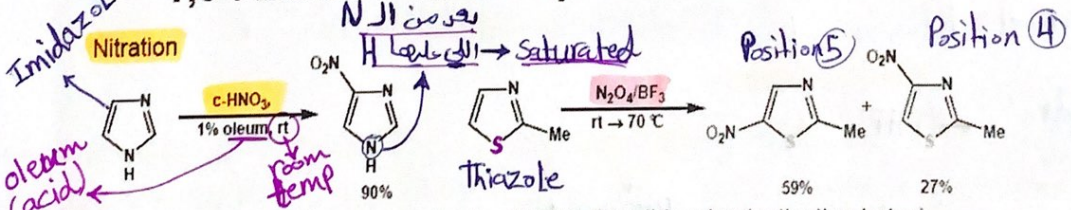
Electrophilic C-Substitution

Reactions of the imidazole carbon atoms occur easily under basic or neutral conditions; however, once protonated, electrophilic substitution is slowed.

Nitration and halogenations of both7V-un-substituted and ./V-substituted imidazoles take place with preferential addition to the 4- or 4- and 5-positions.2

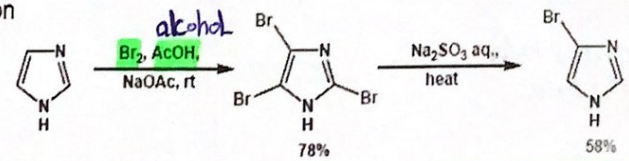


1,3-Azoles – Electrophilic Substitution



- Imidazoles are much more reactive to nitration than thiazoles (activation helps)
- Imidazoles usually nitrate at the 4-position and thiazoles tend to react at the 5-position
- Oxazoles do not generally undergo nitration

Halogenation

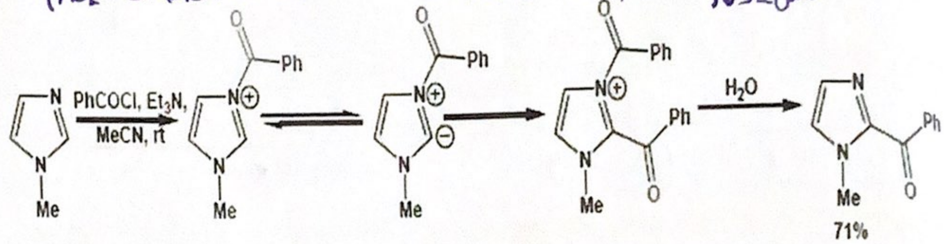


- Imidazoles are brominated easily and bromination at multiple positions can occur
- Thiazole does not brominate easily but 2-alkylthiazoles brominate at the 5-position

Acylation

أولاً تتم على الـ N (not-Stable)

بعدين بصير (resonance) بصير على Position ② (على الـ C مش عالـ N)



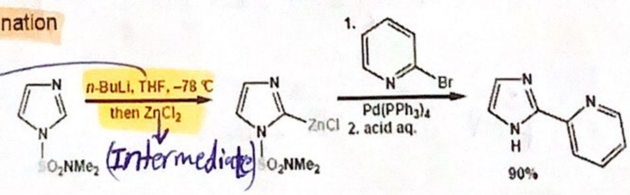
- 1,3-Azoles do not undergo Friedel-Crafts acylation because complexation between the Lewis acidic catalyst and *N* deactivates the ring
- Acylation can be accomplished under mild conditions *via* the *N*-acylimidazolium ylide

1,3-Azoles – Metallation

باخذ بروتون بحط محله (Substitution) معين

Direct Deprotonation

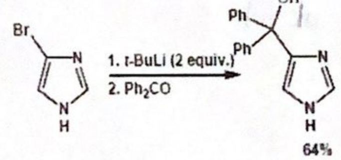
Tetrahydro furan ← (THF)



- Direct deprotonation oxazoles, thiazoles and *N*-alkylimidazoles occurs preferentially at either the 2- or 5-position
- Transmetallation of the lithiated intermediate is possible

Metal-Halogen Exchange

BuLi بحل محل الـ Br بالـ (Intermediate)
بعدين بضيف المركب المطلوب مكانه



- Metallation at the 4-position can be accomplished by metal-halogen exchange
- In the case of imidazoles without substitution at the 1-position, two equivalents of base are required