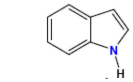
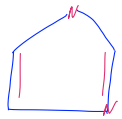
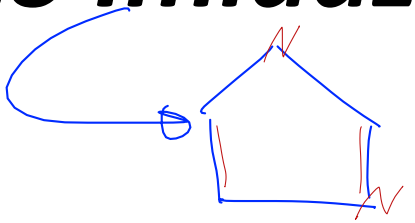




Introduction to Imidazole



حطيتلكم السنوات بالسلايد اللي اجا منه للسؤال

Imidazole is a planar, 5-membered heterocyclic ring containing 2

nitrogen atoms at the 1- and 3-positions. The two nitrogen atoms have

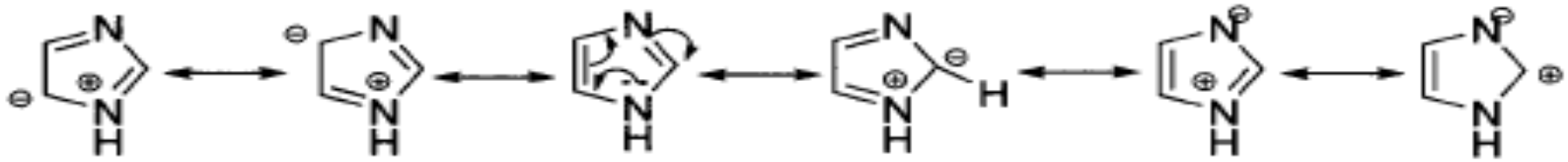
differing reactivities: one like pyridine and the other like pyrrole. Imidazole is a highly polar, water-soluble compound

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

resonance energy in imidazole <<< benzene.

Q30. Which statement about imidazole is FALSE?

A. It is aromatic
B. It is amphoteric
C. It contains two nitrogen atoms
D. It is a 1,3-triazole derivative

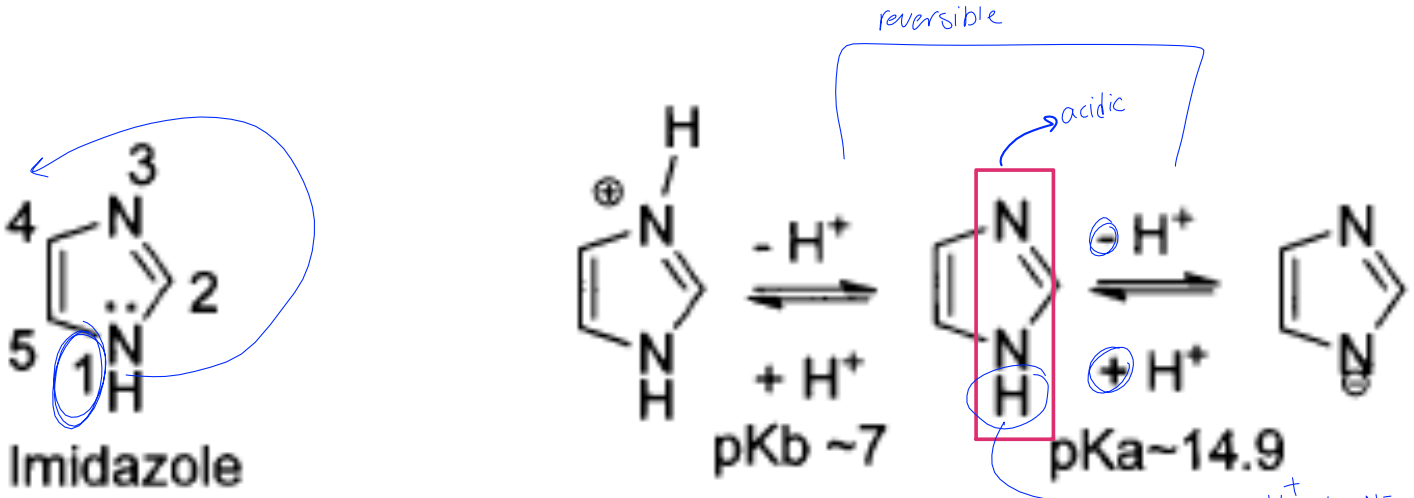


Resonance Structures of Imidazole

- Imidazole is an amphoteric molecule, acting as both an acid and a base. As an acid, it has a pATa 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

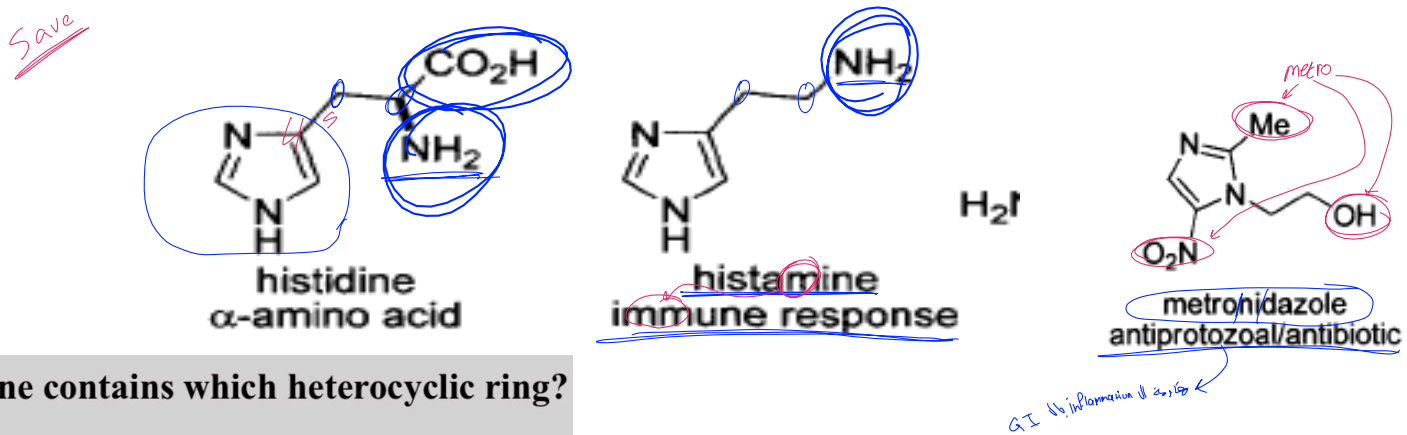
Q3. Imidazole is amphoteric because it:

A. Acts only as an acid
B. Acts only as a base
C. Acts as both an acid and a base
D. Does not react with acids or bases



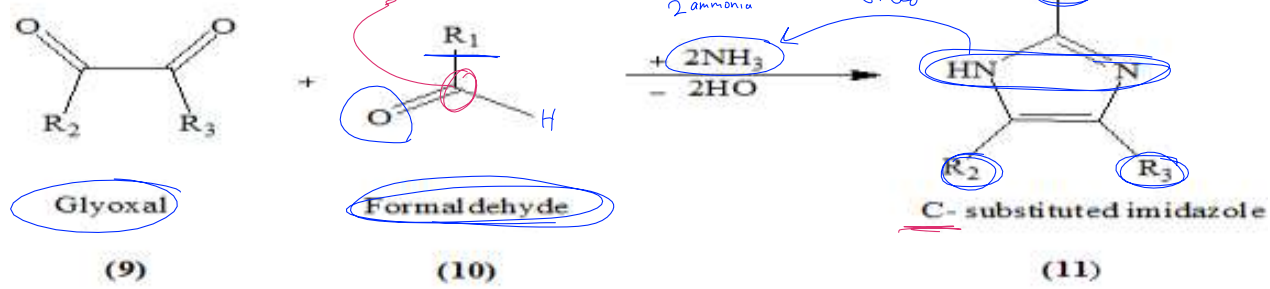
Imidazole Numbering and p*Ka*'s

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



Q35. Histidine contains which heterocyclic ring?

A. Pyridine
B. Thiophene
C. Imidazole
D. Oxazole



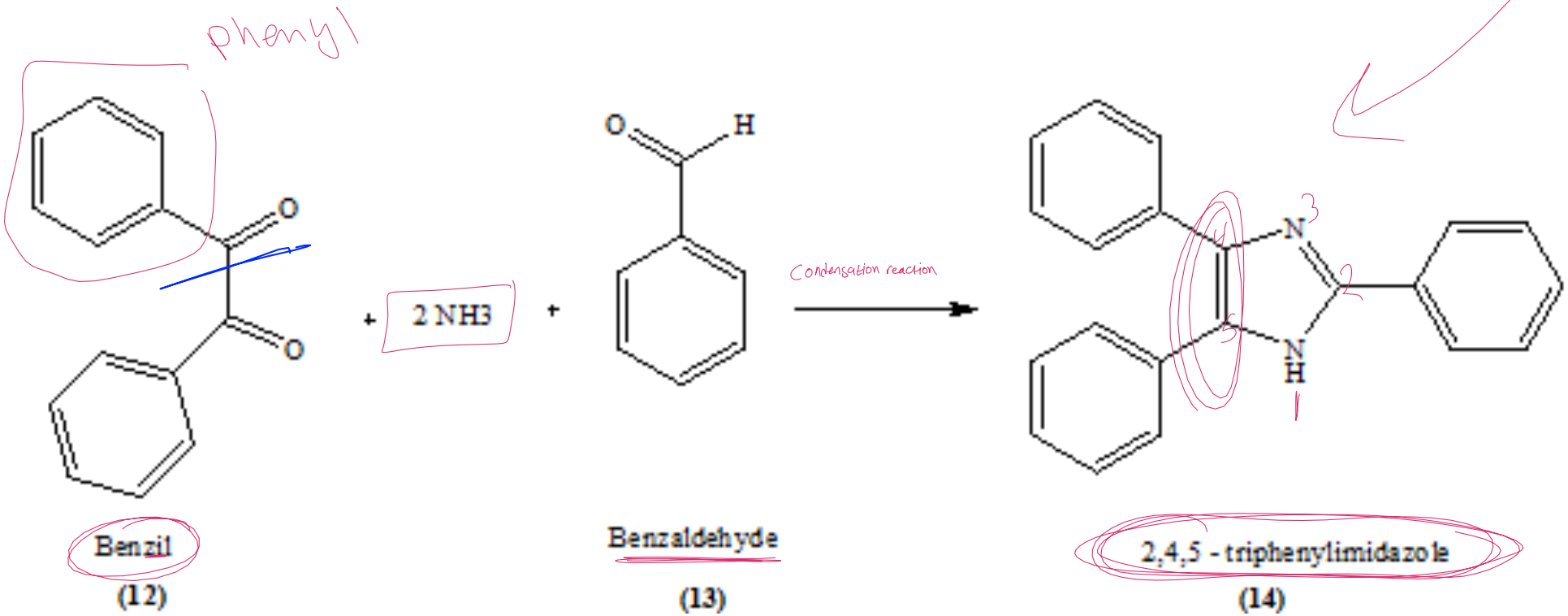
(9) (10) (11)

- **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)**.

Q34. Which reagent is used in Debus synthesis of imidazole?

A. Benzil
B. Glyoxal
C. Acetic anhydride
D. Maleic anhydride

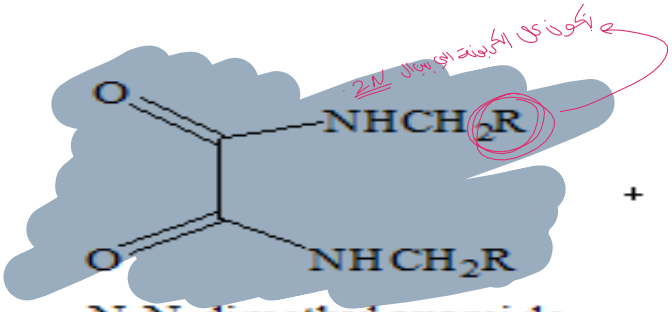
- **2) Radiszewski Synthesis:**
  Radiszewski reported the condensation of a dicarbonyl compound, benzil **(12)** and a- ketoaldehyde, benzaldehyde **(13)** or a-diketones in the presence of ammonia, yield 2, 4, 5-triphenylimidazole **(14)**. [18]



Q36. Which synthesis produces 2,4,5-triphenylimidazole?

A. Debus synthesis
B. Wallach synthesis
C. Radiszewski synthesis
D. Paal–Knorr synthesis

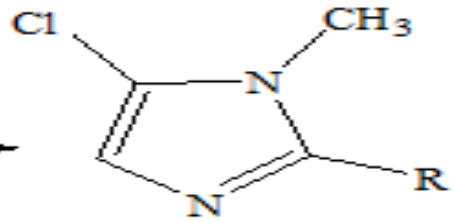
- **Wallach Synthesis:-**
  Wallach reported that when N, N-dimethyloxamide **(18)** is treated with phosphorus pentachloride, a chlorine containing compound **(19)** is obtained which on reduction with hydroiodic acid give N-methyl imidazole **(20)**. Under the same condition N, N-diethyloxamide is 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.



N,N-dimethyloxamide

(18)

+ PCl5

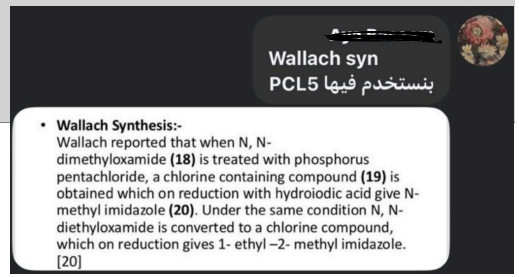


Chlorine containing compound

(19)

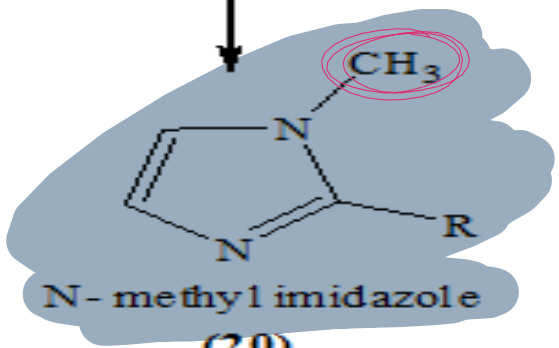
Q14. Which synthesis of imidazole involves phosphorus pentachloride (PCl_5)?

A. Debus synthesis
B. Radiszewski synthesis
C. Wallach synthesis
D. Paal–Knorr synthesis



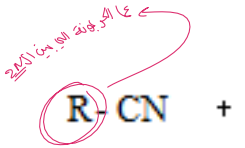
reduction

HI



N-methyl imidazole

(20)



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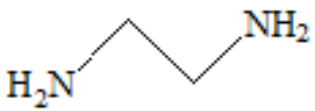
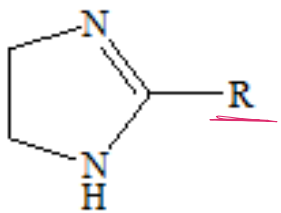


CS_2 / MW



Alkyl cyanide

ethylenediamine

2-substituted 2-imidazolines

(36)

(37)

(38)

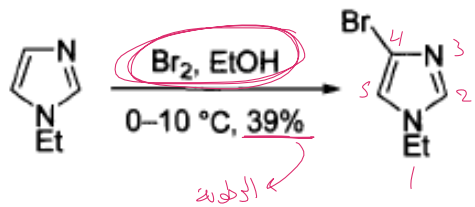
Reactivity of the Imidazole Ring

- *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.

② 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 both N-un-substituted and N-substituted imidazoles take place with preferential addition to the 4- or 4- and 5-positions.2



* furan, pyrrole, thiophene ⇒ like α-position.

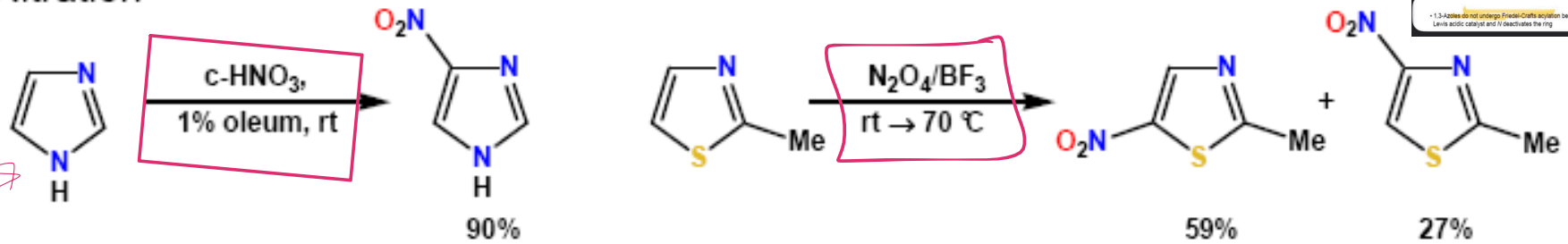
* imidazole ⇒ like 4,5 position.

Q20. Which of the following reactions is NOT undergone by imidazole?

A. Nitration
B. Halogenation
C. Friedel–Crafts acylation
D. Electrophilic substitution

1,3-Azoles – Electrophilic Substitution

Nitration

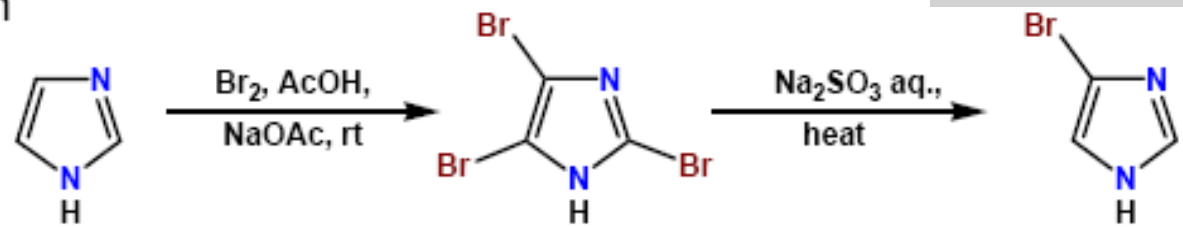


- Imidazoles are much more reactive to nitration than thiazoles (activation helps)
- Imidazoles usually nitrate at the 4-position and thiazoles tend to react at the 5-position
- Oxazoles do not generally undergo nitration

Q28. Which position in imidazole is most susceptible to electrophilic substitution?

A. C-2
B. C-4
C. C-5
D. N-1

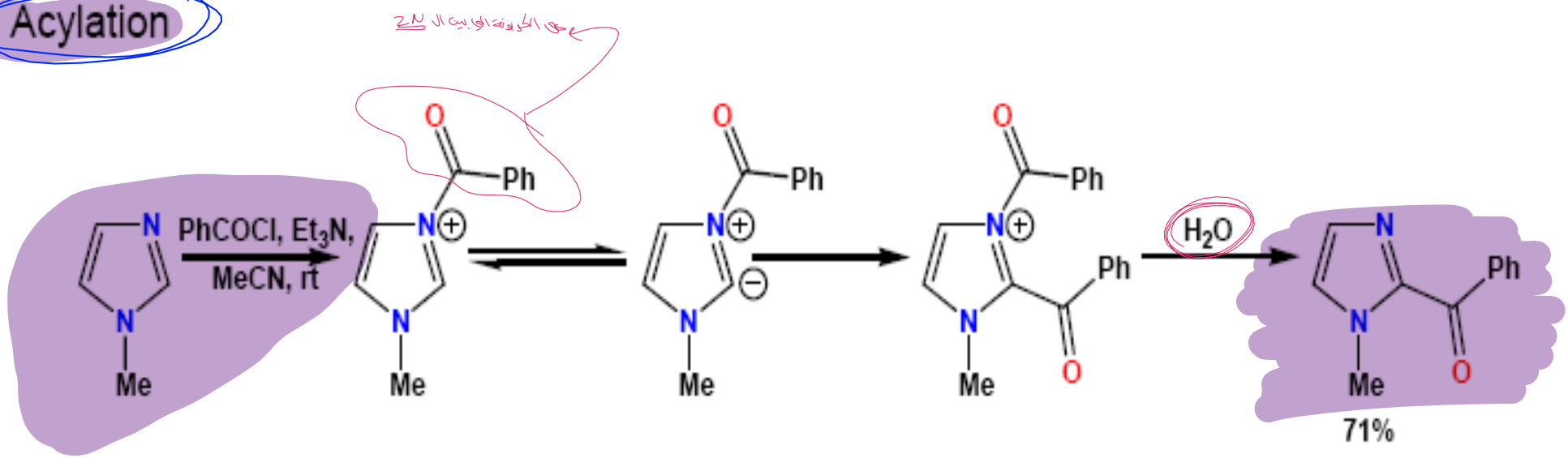
Halogenation



- 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 = Ph = imidazol

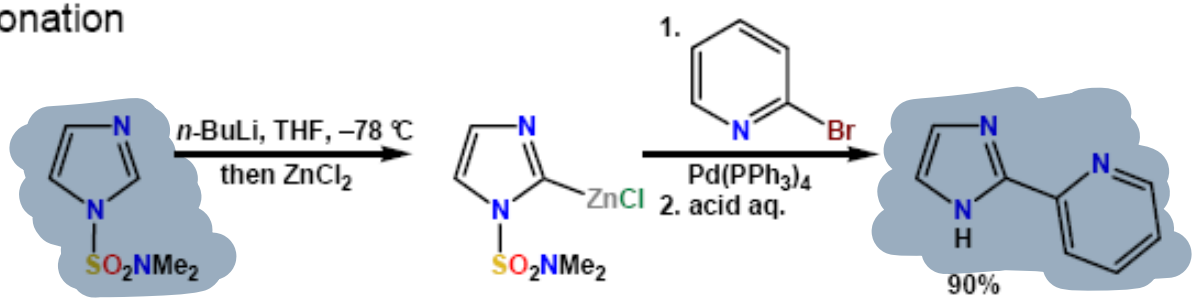
Acylation



- 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

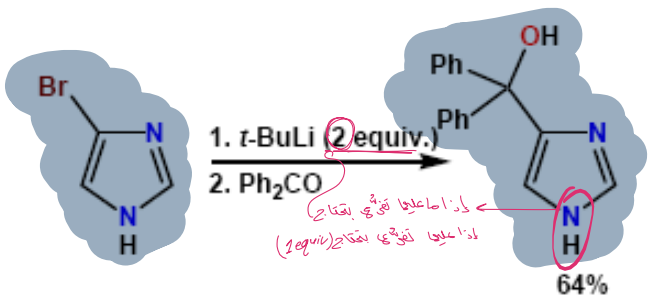
1,3-Azoles – Metallation

Direct Deprotonation



- 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



- 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