Introduction to Imidazole

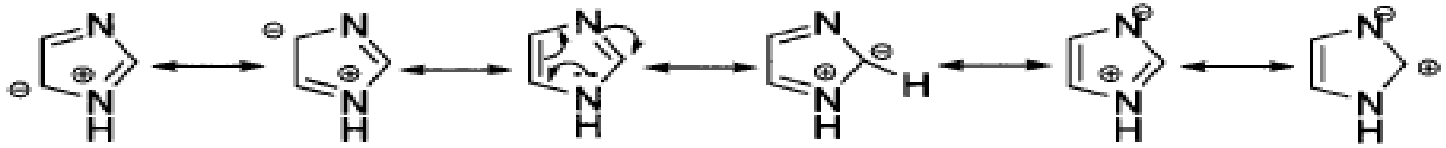
Imidazole is a planar, 5-membered heterocyclic ring containing 2 nitrogen atoms at the 1- and 3-positions. The two nitrogen atoms have differing reactivities: one like pyridine and the other like pyrrole. Imidazole is a highly polar, water-soluble compound

→ lone pair not react with ring

→ react with ring

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

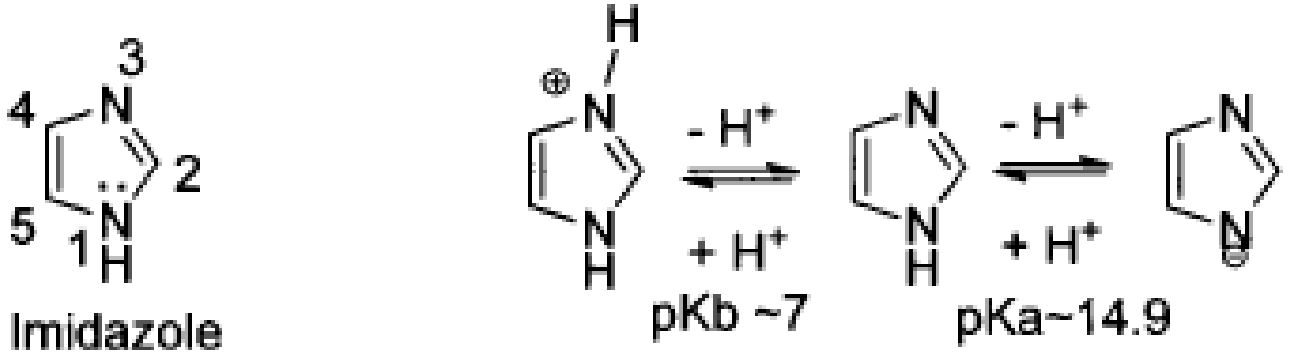
→ pyrrole > furan > thiophene > benzene > imidazole



Resonance Structures of Imidazole

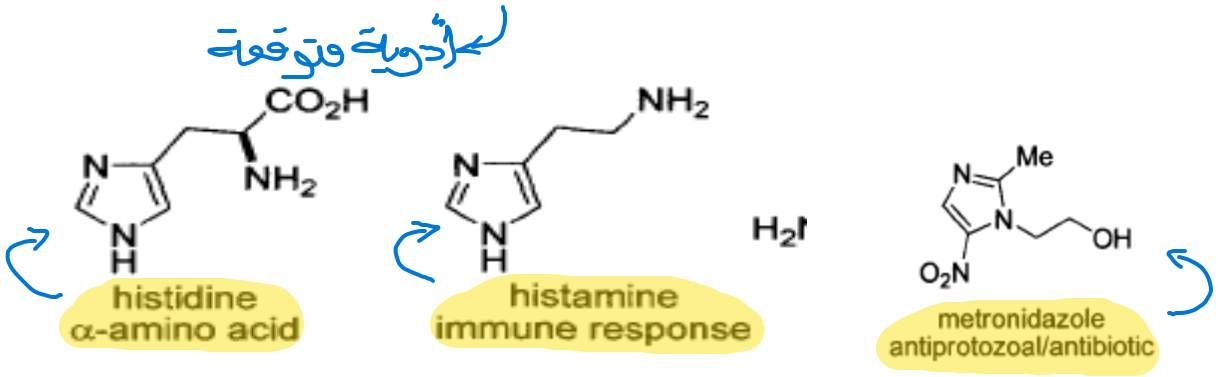
إذا حطيت مع حمض بيشتغل كقاعدة وإذا حطيت مع قاعدة بيشتغل كحمض

- 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

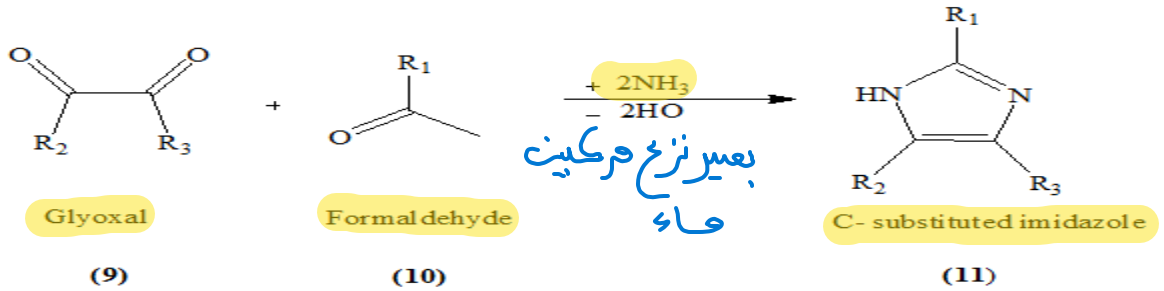


Imidazole Numbering and p*K*a's

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



imidazole تلات طرق لتصنيع
بس هنا الطرق الوحيدة لتصنيعه



(9) (10) (11)

بعيد نزع مركبين ماء

- **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]

  ↳ substituted in carbon atom

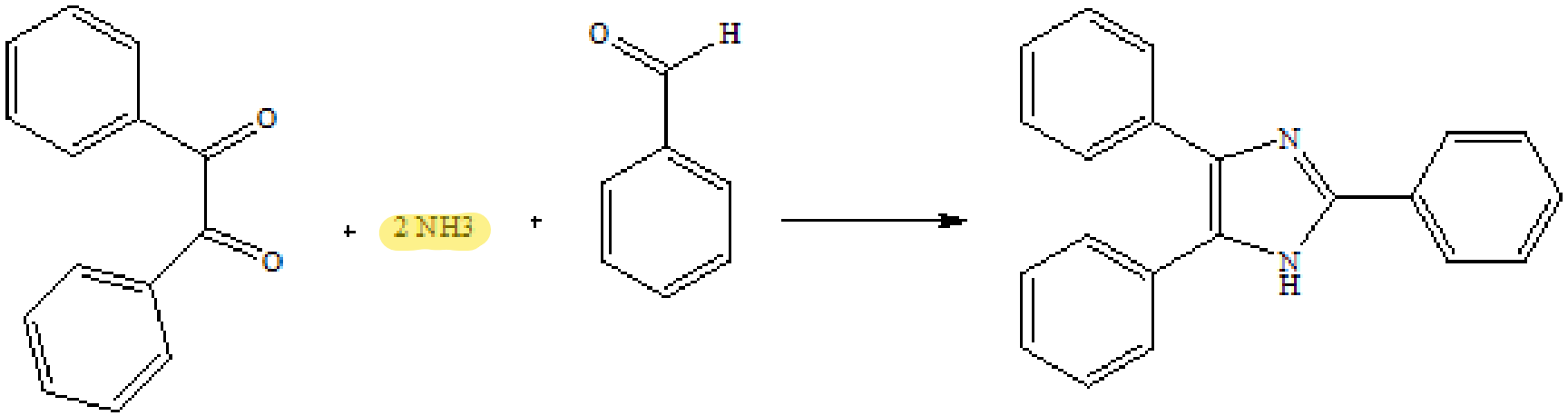
  يعني الناتج بكون أقل من المتوقع

  مع هيك لا يزال الاستخدام هذه الطريقة شائعًا

- **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]

  ↳ contain two Ketone group

  product



Benzil
(12)

Benzaldehyde
(13)

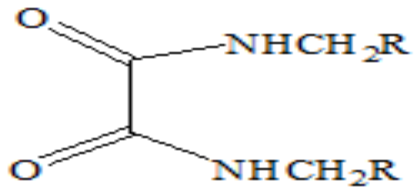
2,4,5 - triphenylimidazole
(14)

benzil + α-diketone + NH_3 ⟶ substituted imidazole

- **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]

  حسب تقرير فاثان وآخرون

- 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.

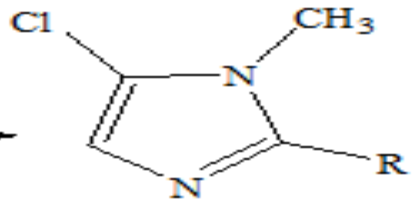


N,N-dimethyloxamide

(18)

\+ PC15

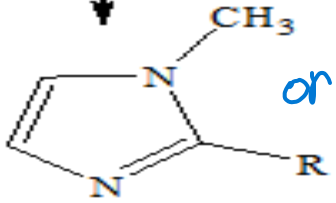
phosphorus pentachloride



Chlorine contaning compound

(19)

HI reduction with hydroiodic acid



N-methyl imidazole

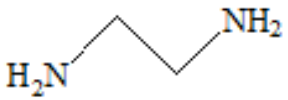
or 1-methyl-2-ethyl imidazole

(20)

Alkyl cynide

(36)

\+



ethylenediamine

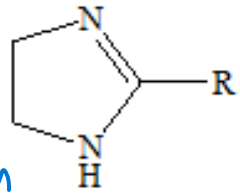
(37)

carbon disulfide

CS_2

MW

microwave irradiation



2-substituted 2-imidazolines

(38)

product of this reaction is high and time of reaction reduced (يقلل)

Reactivity of the Imidazole Ring

إضافة مجموعة حيثيل أو ايثيل إلى ذرة النيتروجين

- *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.

SN2', SN2 تعتمد على

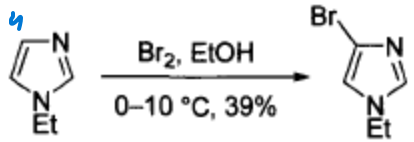
آليات عمليات الألكلة لحركب imidazole.

إذا في ازدحام فراغي بسبب مجموعات كبيرة حول النيتروجين بصير التفاعل أبطأ

Electrophilic C-Substitution

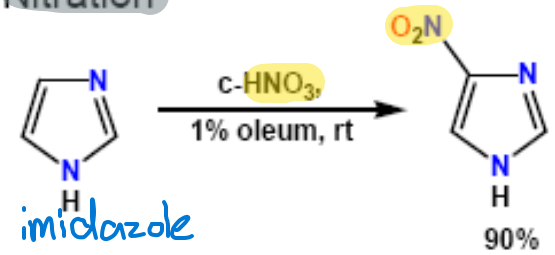
Reactions of the imidazole carbon atoms occur easily under basic or neutral conditions; however, once protonated, electrophilic substitution is slowed.

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

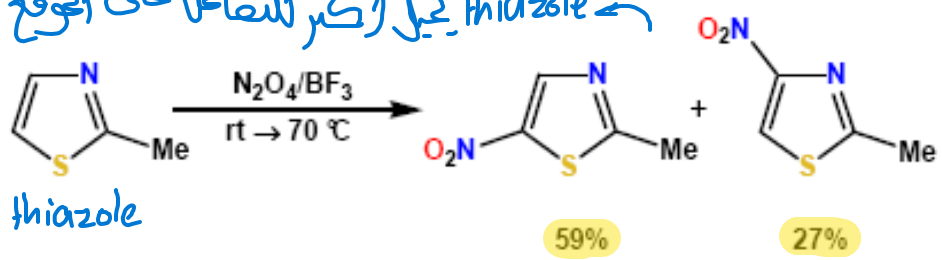


1,3-Azoles – Electrophilic Substitution

Nitration



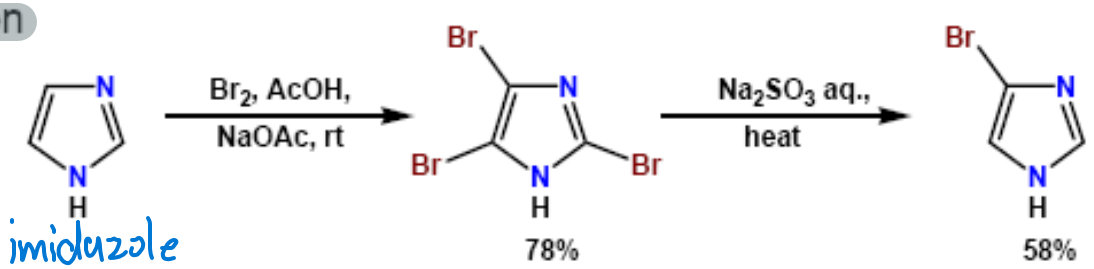
thiazole يميل أكثر للتفاعل على الموقع 5



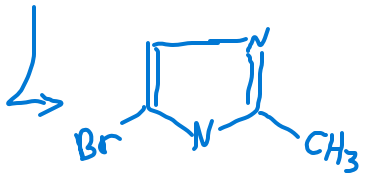
- Imidazoles are much more reactive to nitration than thiazoles (activation helps)
- Imidazoles usually nitrate at the 4-position and thiazoles tend to react at the 5-position
- Oxazoles do not generally undergo nitration

N و O مجموعة

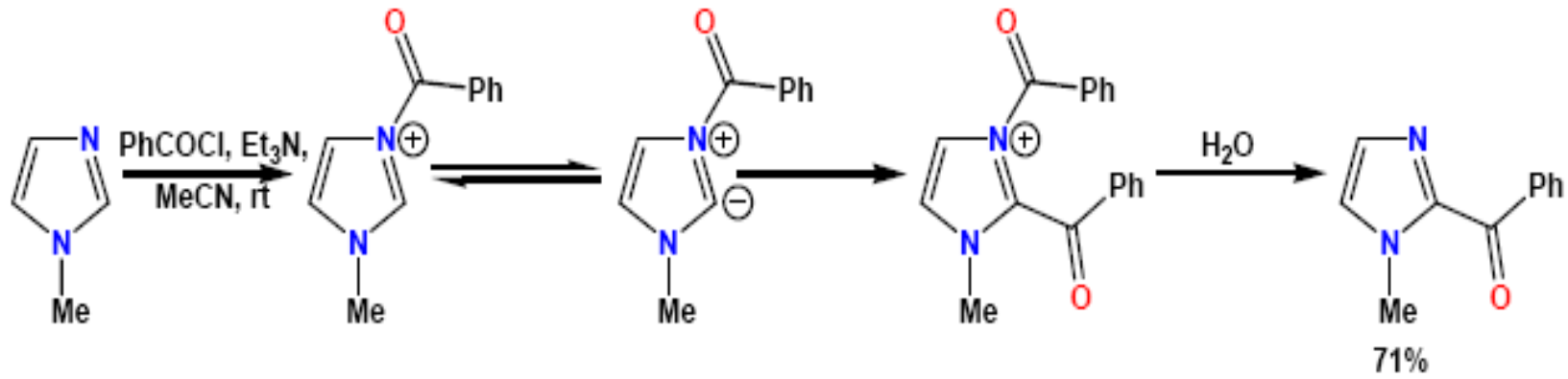
Halogenation



- 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



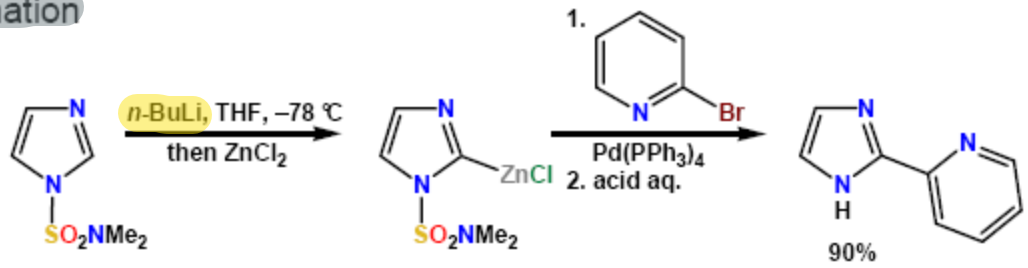
لازم يكون في التفاعل حمض لويس واحنا حكينا ما بصير التفاعل بوسط حمضي

- 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

يعني مجموعة الأسيل على النيتروجين

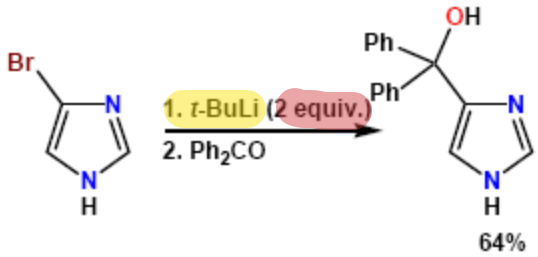
1,3-Azoles – Metallation

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

مركب حلقي فيه ثلاث ذرات N

مركب حلقي فيه أربع ذرات N

Triazoles and Tetrazoles

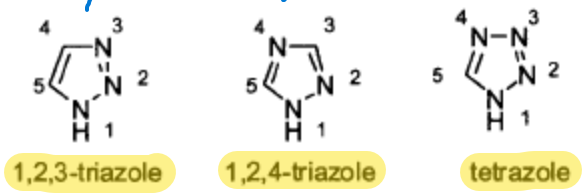
Triazole refers to either one of two isomeric five-member ring compounds with molecular formula $C_2H_3N_3$.

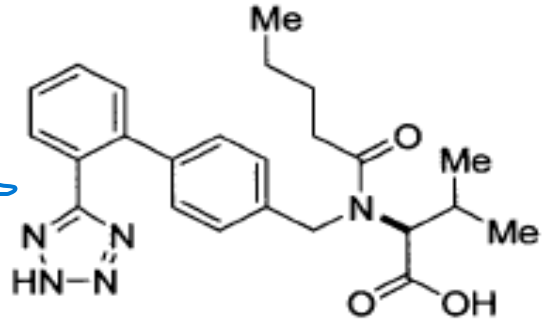
triazole إله شكلين هما:

1,2,3-triazole is a colorless low melting solid with a melting point of 23-25 °C and a boiling point of 203 °C/752 mmHg, while the 1,2,4-triazole is a colorless crystalline solid with a melting point of 119-121 °C. Both compounds are corrosive and an irritant to both skin and eyes. Triazole is a five-membered aromatic heterocycle with three N heteroatoms.

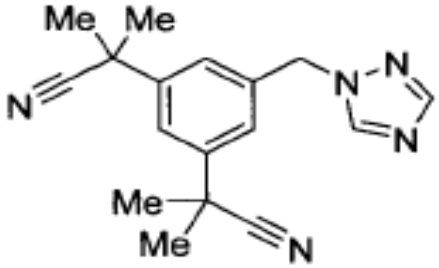
Tm لهذا الشكل أعلى بكثير

isomer لبعض

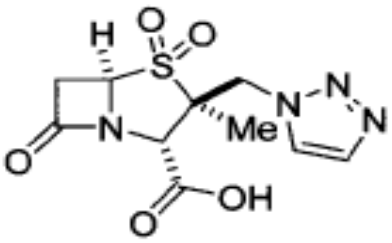




valsartan (Diovan)



anastrozole (Arimidex)

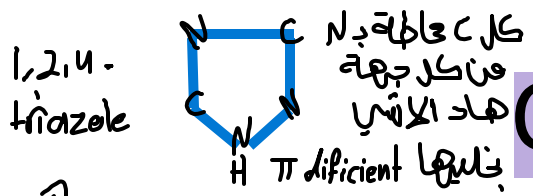


tazobactam (Zosyn)

Triazoles and tetrazoles do not exist in nature. However, many synthetic medicines do contain triazoles and tetrazoles.

- valsartan, an angiotensin receptor blocker (ARB) indicated for treatment of high blood pressure and other cardiovascular disease contains a tetrazole.

- Anastrozole contains a 1,2,4-triazole and is an aromatase-inhibiting drug approved for treatment of breast cancer.
- Tazobactam is a 1,2,3-triazole containing compound that inhibits the action of bacterial ß-lactamases and is used to treat bacterial infection in combination with the beta-lactam antibiotic piperacillin



Chemical Reactivity

- Both carbon atoms in 1*H*-1,2,4-triazoles are π deficient because both are attached to electronegative nitrogen atoms and the electron density (0.744) at both carbon atoms is low and susceptible to nucleophilic substitution under mild conditions.
- It is a weak base and the pK_a of 2.19 is for protonated species. The NH-protons in *N*-unsubstituted-1,2,4-triazoles are acidic in nature.
- The pK_a of 1,2,4-triazoles is 10.26.
- The triazolium ions formed are also prone to nucleophiles.
- Electrophilic substitution takes place only at nitrogen atoms because of high electron density.

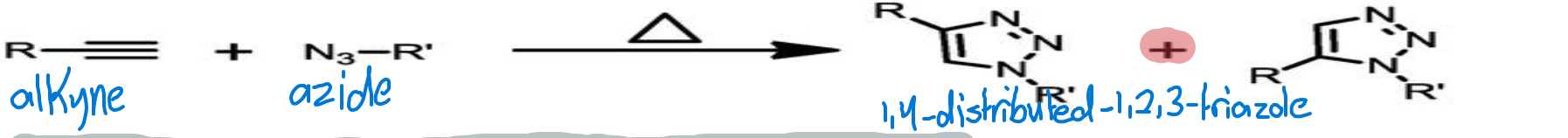
- 1,2,4-Triazole effectively contains two pyridine type atoms and one pyrrole type nitrogen atom. It is deactivated against electrophilic attack and thus resembles pyridine. Nitration, sulfonation and *N*-oxidation do not occur with simple triazoles. Triazolate anions, however, do react readily with electrophiles, alkylation and acylation being the reactions that have been most investigated

- Huisgen 1,3-dipolar cycloaddition 1,3-dipolar cycloaddition of alkynes to azides
- to form l,4-disubsituted-l,2,3-triazoles.

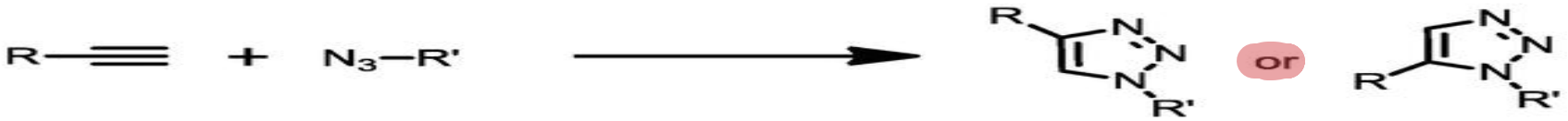
- Metal-catalyzed 1,3-dipolar cycloaddition
- Strain-promoted azide alkyne cycloaddition

حفظ المعادلات اسم وستركشر

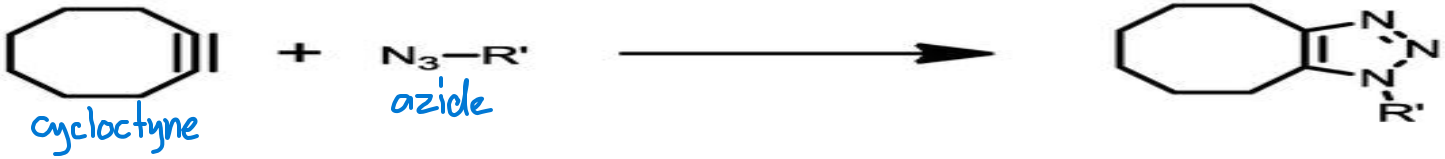
(i) Huisgen 1,3- dipolar cycloaddition



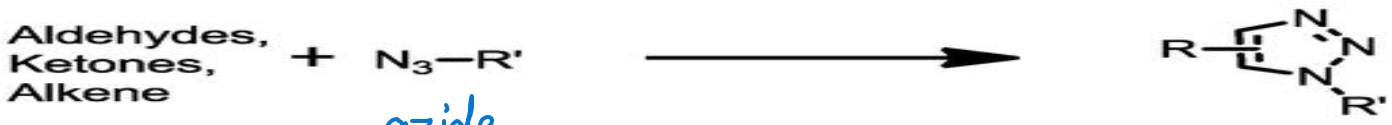
(ii) Metal catalyzed 1,3- dipolar cycloaddition



(iii) Strain promoted azide alkyne cycloaddition



(iv) Metal free synthesis of 1,2,3-triazoles



Construction of the Tetrazole Ring

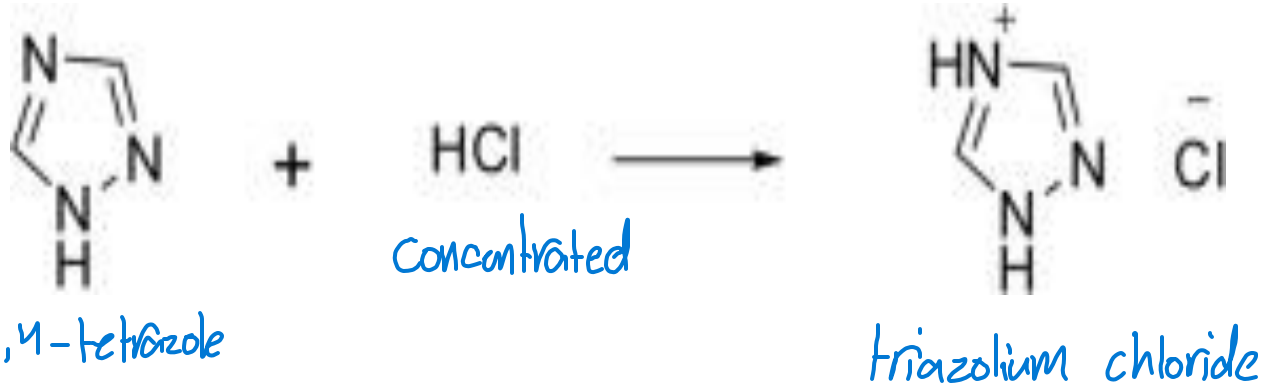
- The synthesis of tetrazole usually involves a variation of the Finnegan tetrazole synthesis that is the addition of hydrazoic acid to a carbon-nitrogen multiple bond.

carbon-nitrogen multiple

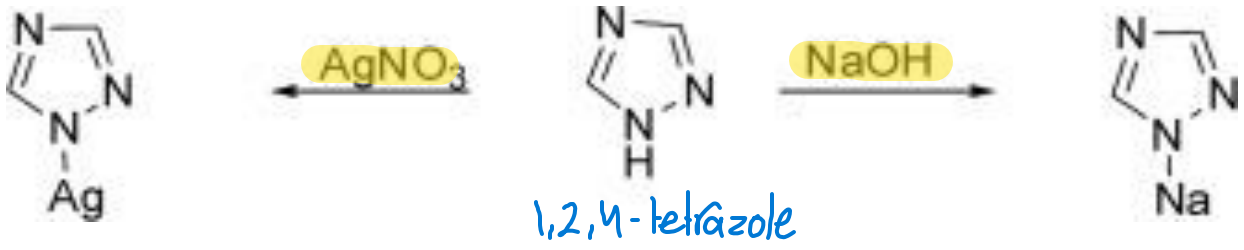
hydrazoic acid

1,5-substituted-tetrazole

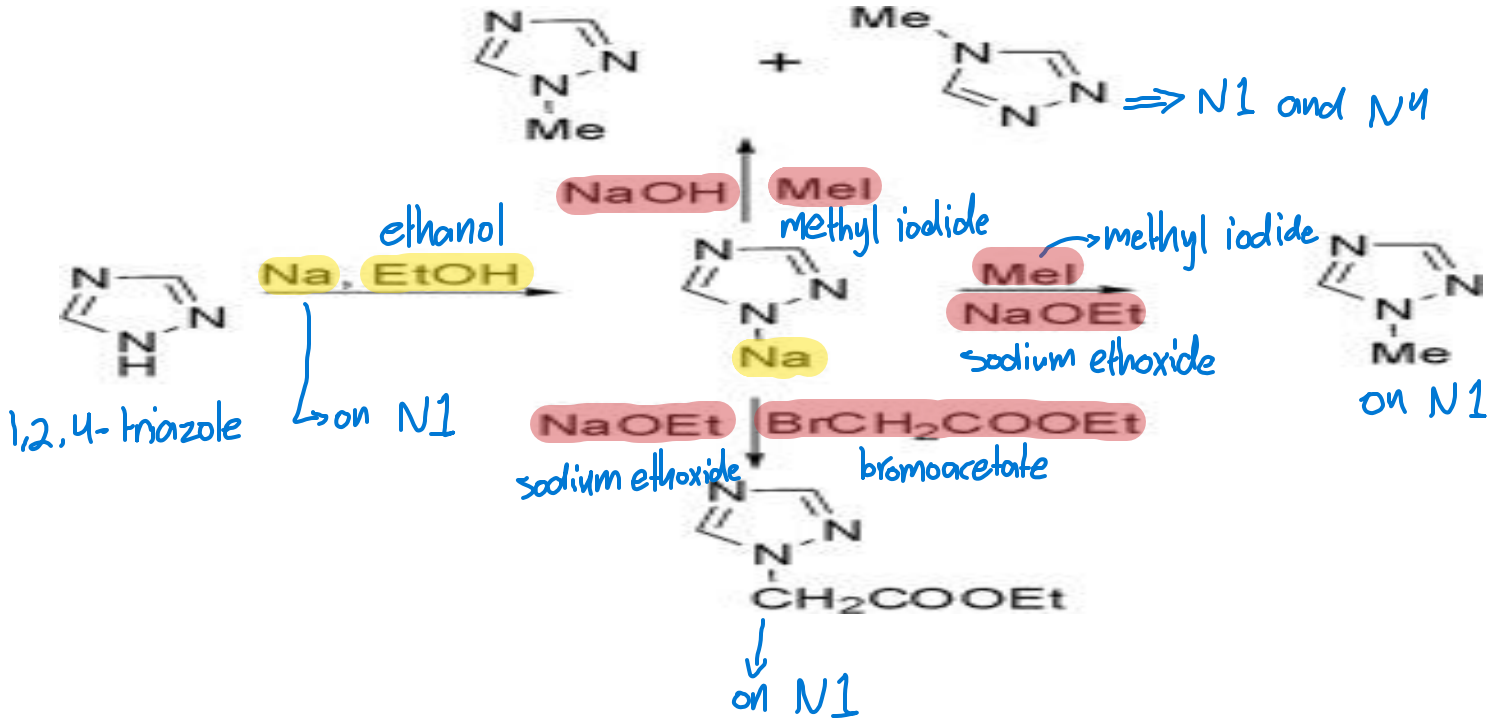
- Electrophilic Substitution Reactions
- The parent 1*H*-1,2,4-triazole is readily protonated at position 4 in concentrated HCl to form triazolium chloride.



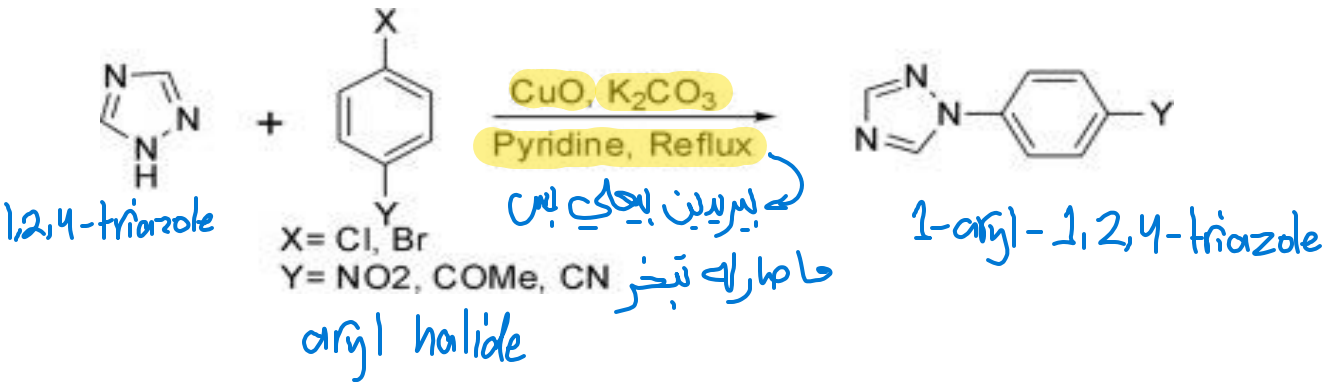
- Metalation
- 1*H*-1,2,4-Triazoles are easily metalated with NaOH, $AgNO_3$, and copper nitrate to form respective organometallic compounds. → organic compound with metal
-



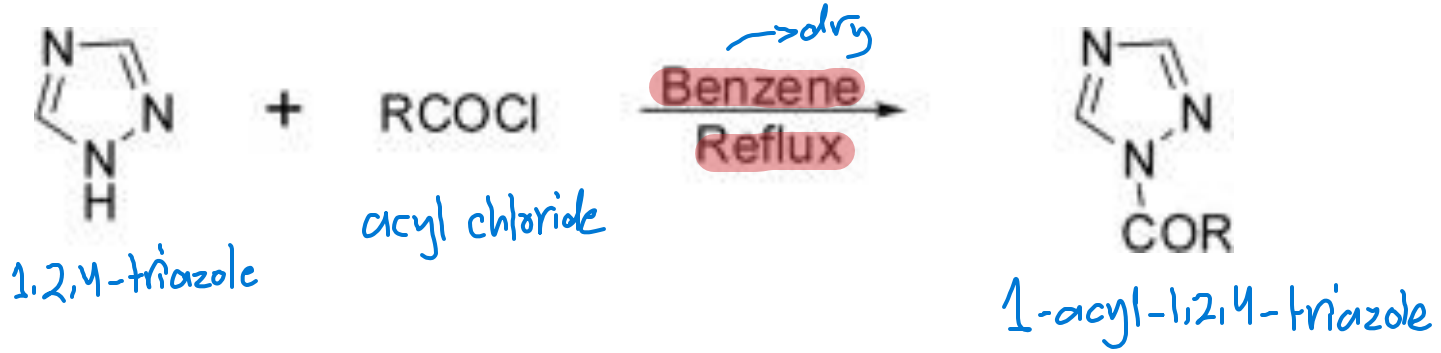
- Alkylation[693]
- 1*H*-1,2,4-Triazole is regioselectively
- alkylated at N_1 when sodium ethoxide in ethanol is used as a base
- but alkylation in aqueous NaOH with methyl sulfate gave a mixture of 1-methyl- and 4-methyl-1,2,4-triazole.
- Alkylation with ethyl chloroacetate in sodium methoxide produced N_1-substituted products.



- Arylation Reactions[695] → add aryl group to 1,2,4-triazole
- 1*H*-1,2,4-Triazoles are arylated with aryl halide having an electron-withdrawing substituent (Cl, Br) under Ullmann conditions using CuO as catalyst in refluxing pyridine, which offered 1-aryl-1,2,4-1*H*-triazole.



- Acylation
- 1*H*-1,2,4-Triazole on reaction with acyl chloride in dry benzene under reflux delivered 1-acyl-1,2,4-triazole.



Electrophilic Substitution at Carbon

- Bromination of 1*H*-1,2,4-triazoles in aqueous NaOH solution occurs readily at room temperature to give 3,5-dibromo-1,2,4-triazole in 82% yields. However, chlorination in aqueous $KHCO_3$ solution delivered 1-chloro-1,2,4-triazole, which either on heating or long storage rearranged to 3-chloro-1*H*-1,2,4-triazole in 40% yields.
-