

3(N) ←

Triazoles and Tetrazoles

4(N) →

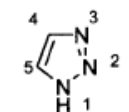
Triazole refers to either one of two isomeric five-member ring compounds with molecular formula

$C_2H_3N_3$. *Triazole هو مركب ثلاثي الحلقة*

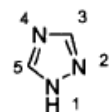
1,2,3-triazole is a colorless low melting solid with a melting point of 23-25 °C and a boiling point of 203 °C/752 mmHg, while the **1,2,4-triazole** is a colorless crystalline solid with a melting point of 119-121 °C. Both compounds are *corrosive (ضار)* and an irritant to both skin and eyes. Triazole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

لوجود ال N وبذلك يكون قاعدي

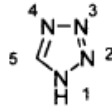
مركب الحلقية



1,2,3-triazole



1,2,4-triazole



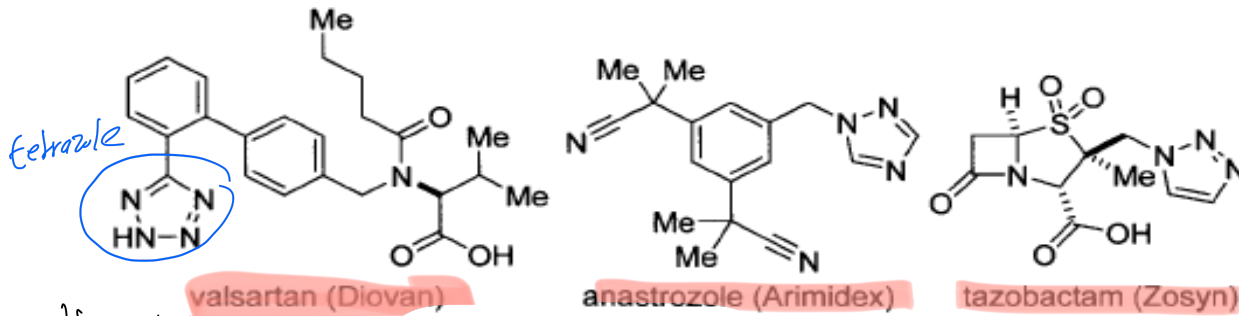
tetrazole

Triazole (Five-membered ring with 3 N)
 $C_2H_3N_3$

↓
1,2,3-triazole
① colorless
② low melting point (23-25)
③ B.P = 203 °C / 752 mmHg

1,2,4-triazole
① colorless
② crystalline solid
③ melting point = (119-121)

↑
corrosive & irritant



مستحقو جوائز با لبيب -

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

بعض أمراض القلب وارتفاع ضغط الدم

بعض التركيبات الدوائية

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

بعض سرطانات الثدي
aromatase

• **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 β -lactamases and is used to treat bacterial infection in combination with the beta-lactam antibiotic piperacillin

دواء يتم استخدامه مع piperacillin لعلاج عدوى الجهاز الهضمي

التركيب

مستحقو

للحفظ

1

$\downarrow$ B-lactamase enzyme

عبارة عن إنزيم تقوم البكتيريا بتركيبه لتكسير المضادات الحيوية

2

فكس السكيدية الجايين عنه تتجوق ختره

ضائف

Triazole - 294 و 1 ج

1

Weak Base

2 عنه عنا كربونيت و 3N ، و ال N اى كورساليين من الكربون و 2 يهـ ال N صبي الكرونة الكربون و بالتالي الكربون يصعب فقير بالكرونة (π deficient) و يصعب الكرونة على كانه الكرونة قليلة و بالتالي هي تعبر electrophile و تقوم بتفاعلات nucleophilic substitution rxns

3

1,2,4-triazoles

الي نيو N-H

قد ينفصل H^+ و يصعب ال acidic .

4



موجب الشحنة

معاد electrophile و بعد تفاعلات nucleophilic substitution rxns.

5

electrophilic substitution rxns

كانت تفاعل ال N عنه خبي بالكرونة خفوة ال صبي الكربون فاموز N nucleophile و بعد تفاعلات electrophilic substitution rxns.

معلومة

6

1,2,4 - triazole

(3N)osis



1(N)



Pyrrole-Type



هو اذى فيه e^- فيه باء الاله
و فيه فاعل H^+ و فاعل
quaternary Li^+ , Na^+ , protonation



2(N)



Pyridine-type



هو اذى يكون اذى فيه e^- خاير
Ring ال و فاعل H^+
quaternary Li^+ , Na^+

7

simple triazoles ← هو ال ال

ال ال ال ال ال ال ال ال

8

Triazole anion
هو ال ال ال ال ال ال ال ال

electrophilic substitution rxns

al triazole ال ال

هو ال ال ال ال ال ال ال ال
nucleophilic substitution rxns
acylation ال ال alkylation ال

هو ال ال ال ال ال ال ال ال
electrophilic substitution rxns
electrophilic substitution rxns

nitration or sulfonation
or N-oxidation

- 
- Both carbon atoms in 1H-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 تفاعلی مع nucleophile 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. پذیرد
 - 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.

المركب
هو
مستقر
electrophilic
subst
Triazolate anions, however, do react readily with electrophiles, alkylation and acylation being the reactions that have been most investigated

طرائق تحضير 1,2,3-triazoles

كان
من قبل
الطريقة

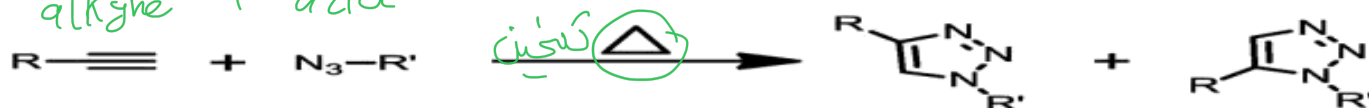
- Huisgen 1,3-dipolar cycloaddition 1,3-dipolar cycloaddition of alkynes to azides
- to form 1,4-disubstituted-1,2,3-triazoles.

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

(i) Huisgen 1,3- dipolar cycloaddition

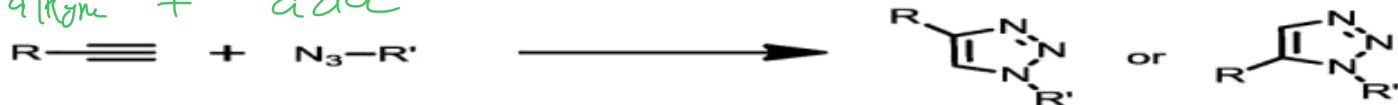
1,2,3-triazole

alkyne + azide

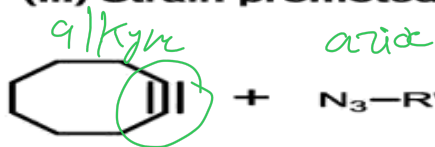


(ii) Metal catalyzed 1,3- dipolar cycloaddition

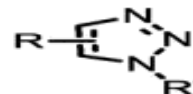
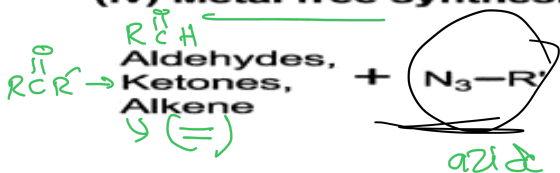
alkyne + azide



(iii) Strain promoted azide alkyne cycloaddition



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



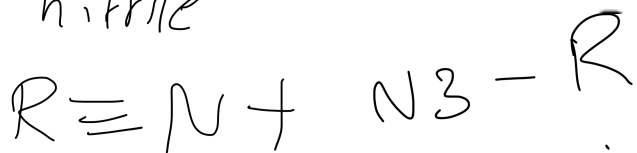
Construction of the Tetrazole Ring

تتزازول / tetrazole

- 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.



nitrile



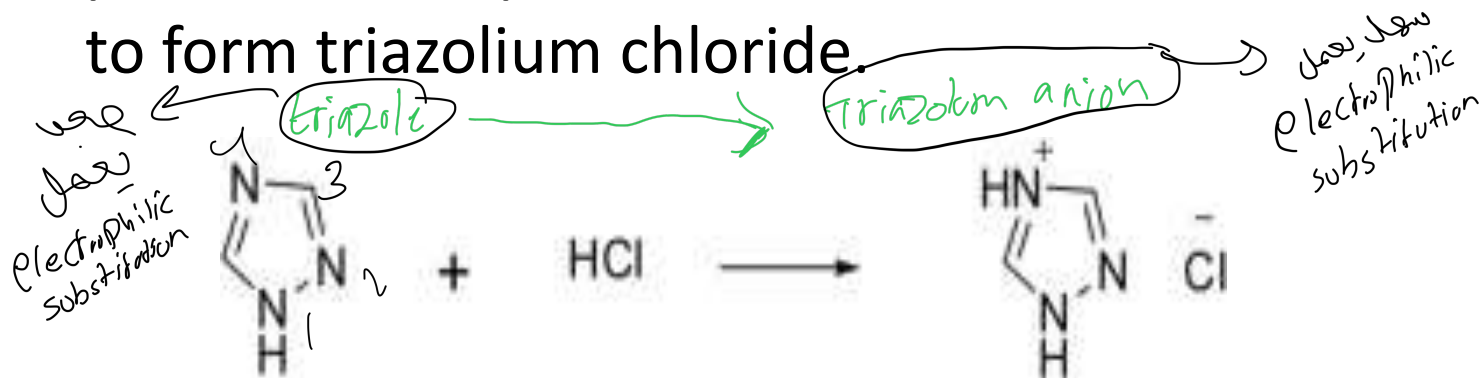
hydrazoic acid



↑
نيتريد
النتروجين
الأكسجين

- Electrophilic Substitution Reactions

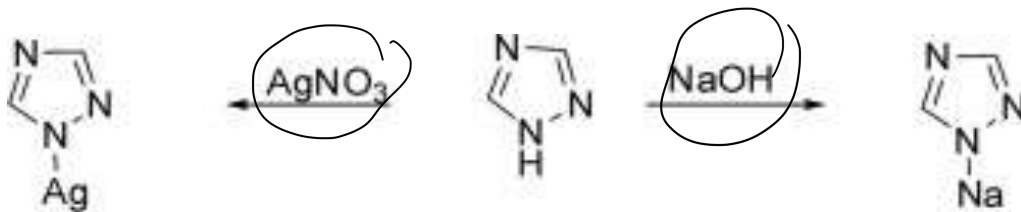
- The parent 1H-1,2,4-triazole is readily protonated at position 4 in concentrated HCl to form triazolium chloride.



① Protonation of N

at position ④

- Metalation
- 1H-1,2,4-Triazoles are easily metalated with NaOH, AgNO₃, and ^{Cu(NO₃)₂} copper nitrate to form respective organometallic compounds.



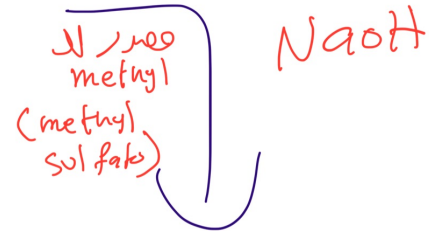
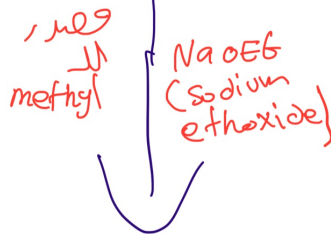
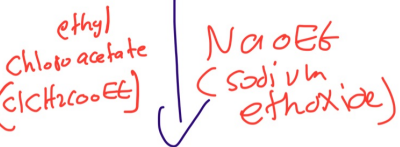
Na و Ag تفاعل
 سافرات و ن و ل

تخليق البازيد في جاي (S_N2) رجوعه مسير :

1,2,4-triazole



Sodium 1,2,4-triazolate



mixture

1-methyl-1,2,4-triazole
base

1-methyl-1,2,4-triazole

4-methyl-1,2,4-triazole

N1-substituted
products.

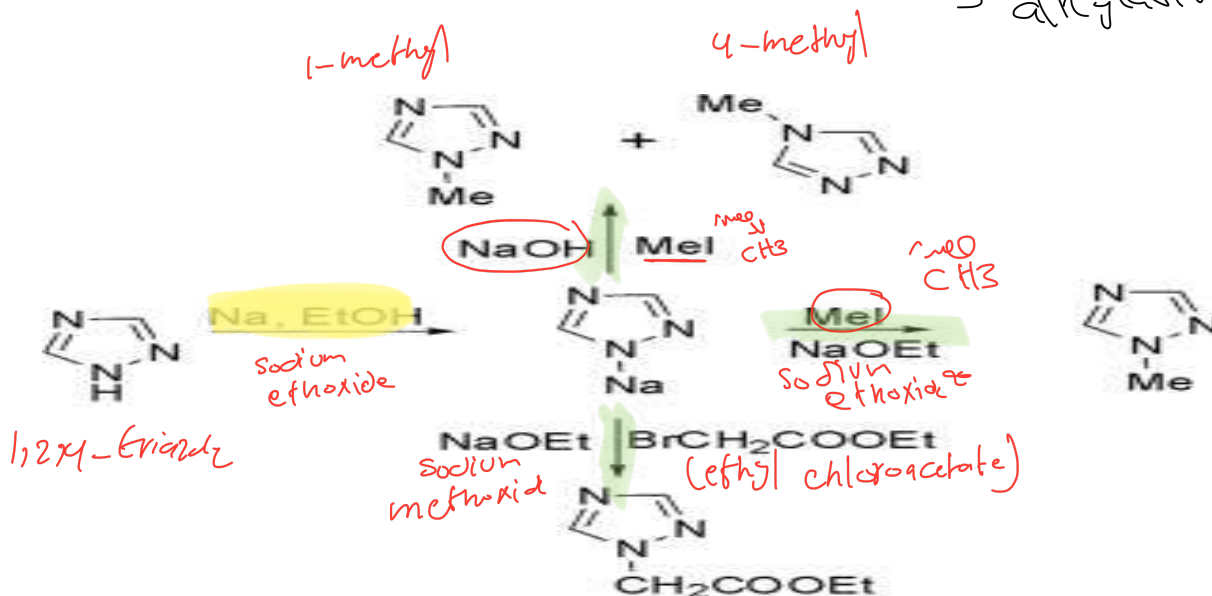
- Alkylation⁶⁹³

- 1H-1,2,4-Triazole is regioselectively
- alkylated at N₁ 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 N₁-substituted products.

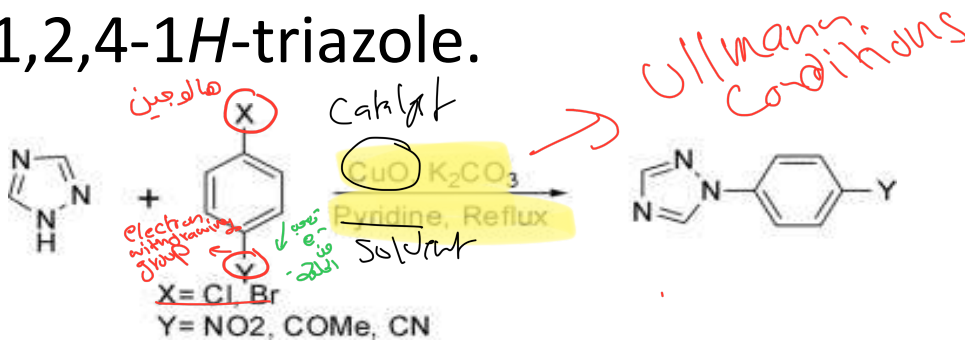
التباعد
ينتج مركب واحد

alkylation
N على

alkylation

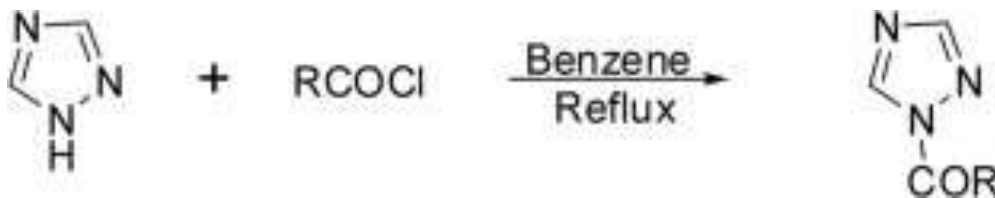


- Arylation Reactions⁶⁹⁵
- 1H-1,2,4-Triazoles are arylated with aryl halide having an electron-withdrawing substituent under Ullmann conditions using CuO as catalyst in refluxing pyridine, which offered 1-aryl-1,2,4-1H-triazole.



1,2,4-Triazole + aryl halide $\longrightarrow$ 1-aryl-1,2,4-Triazole

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

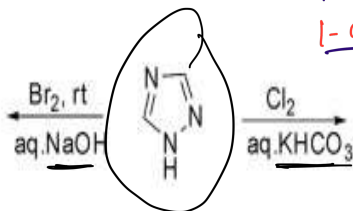
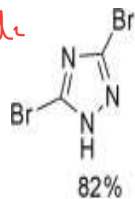


کلسی قبل
کنا نفع علی
ال N راجع
Carbon

Electrophilic Substitution at Carbon

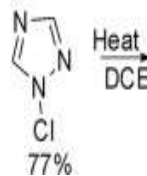
- Bromination of 1H-1,2,4-triazoles in aqueous NaOH solution occurs readily at room temperature to give 3,5-dibromo-1,2,4-triazole in 82% yields. However, chlorination in aqueous KHCO₃ solution delivered 1-chloro-1,2,4-triazole, which either on heating or long storage rearranged to 3-chloro-1H-1,2,4-triazole in 40% yields.

3,5-dibromo-1,2,4-triazole



Basic
condition

1-chloro-1,2,4-triazole



on N



on Carbon

3-chloro-1,2,4-triazole