

Pyrrrole
Pyridine
Imidazole

حلقة خماسية
فيها 2 نيتروجين (N) →

imidazole ⇒ 1,3-diazole



Introduction to Imidazole

فيها 2 نيتروجين
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 6% *electrons and has a* resonance energy of ~ 50 kJ/mol. The resonance energy of imidazole is lower than benzene

حلقة خماسية

1 N على موقع

3 N على موقع

2(N) in Imidazole

Pyrrrole
N على موقع 2

Pyridine
N على موقع 1

الشبيه بـ Pyridine

water Polar
Imidazole highly Polar

حقبة اربعة
Imidazole

Imidazole

فيها 2 نيتروجين

حلقة خماسية
فيها 2 نيتروجين
(N) وموقع على
موقع (1) وموقع (3)

Imidazole

2 N
Pyrrrole
Pyridine

Pyrrrole

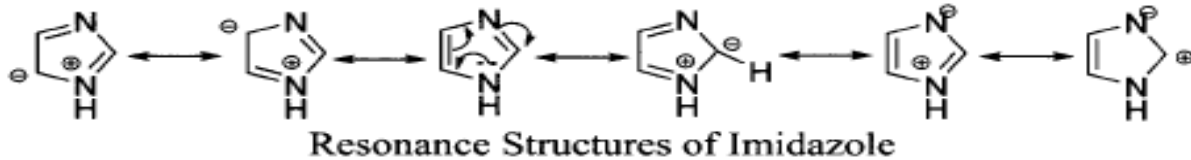
aromatic
cyclic
planar
hukle 3 Rule

water highly polar
Imidazole

5

resonance energy of benzene

resonance energy of Imidazole



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

حماض وقلويات اميدازول

5. اميدازول امفوتريک ہے جس کا $pK_a = 14.9$ ہے اور اس کا $pK_b = 7$ ہے۔

Carboxylic acid > Phenol > Imidazole > alcohols

Imidazole > Pyridine

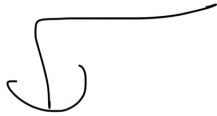
6. اس کا استعمال اس کے اسے اس کے لئے ہے۔

7. اس کا استعمال اس کے اسے اس کے لئے ہے۔



Imidazole

عربي amphoteric
(amphoteric)



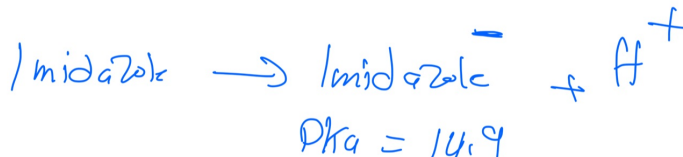
إذا طية بوسط قاسي



يستغل كمل

نؤ بصير:

لا أظ Imidazole بوسط قاسي لا يستغل
كله عفي والحق بيزه او H^+



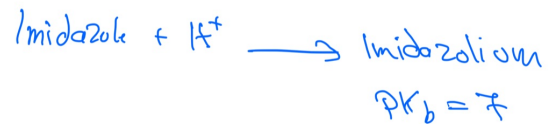
إذا طية بوسط عفي



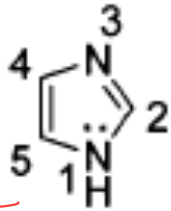
يستغل كقادرة

نؤ بصير:

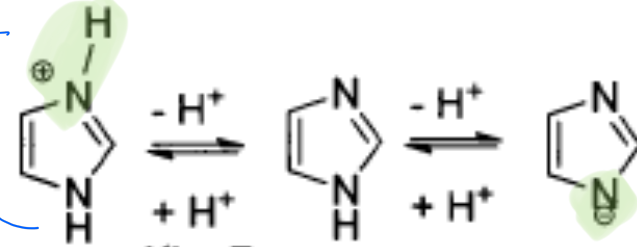
لا أظ Imidazole بوسط عفي فليان بار
 H^+ لا يستغل Imidazole كقادرة ولا
يستغل H^+



imidazole



لو تلاحظ هون ان
N كسبة H^+
ع وكسبة كفاية
معنا اننا حاطين
لبسط عضي .

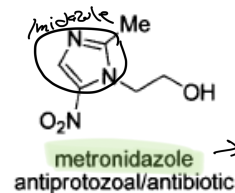
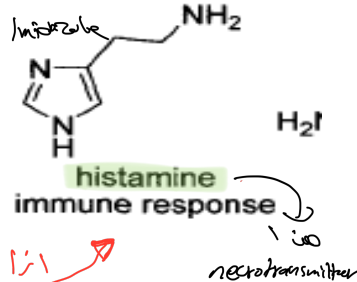
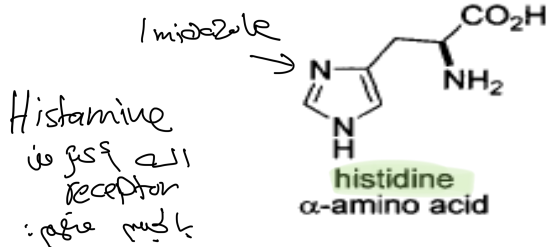


لو تلاحظ هون
ان N تركز
ان H^+ رابعة سالبه
فهي تركز وبتا تاتي
فيها حاط ان
imidazole بوسط
قاعدي

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.

يدخل في تركيب (أدوية) وال amino acids وال neurotransmitters



دواء
للعمل
الطفيليات
في الجهاز الهضمي
GI
و كثير بمره رخيص
و ممكن كثر أخطاء
يعودها على الصبر فيه و ريكالونه
اذا رادهم كذاهم فحش
ولكن هو دواء حسيه
عنه أي دواء في بركيته ل
عنه على الاله $omnibic$ يعز دواء مبرهن
Carcinogenic
drugs

انزاع CO_2H
decarboxylation

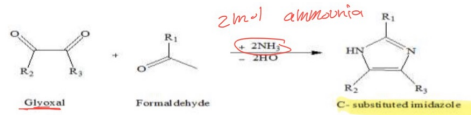
في receptors يرتبط
على histamine
في مسارات المسايكه وها
يرتبطها و تصير عنا اعراض
المسايكه و فلهذا بوي ان عمل دواء
يضعف اعراض المسايكه جدي اعني
histamine receptor antagonist
. alleffing

في receptors يرتبط
على histamine
المسايكه H_2 receptor
انزاع H_2 receptor
يرتبطها و تصير عنا اعراض
المسايكه و فلهذا بوي ان عمل دواء
يضعف اعراض المسايكه جدي اعني
histamine receptor antagonist
. alleffing

دو جزو 3 ایدیت بی جایست :

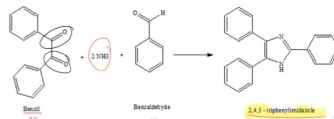
طرز تهیه آن : imidazole

① Debus :



glyoxal (1,2-dicarbonyl) + Formaldehyde $\xrightarrow{2\text{NH}_3}$ C-substituted imidazole (low yields)

② Radiszewski :



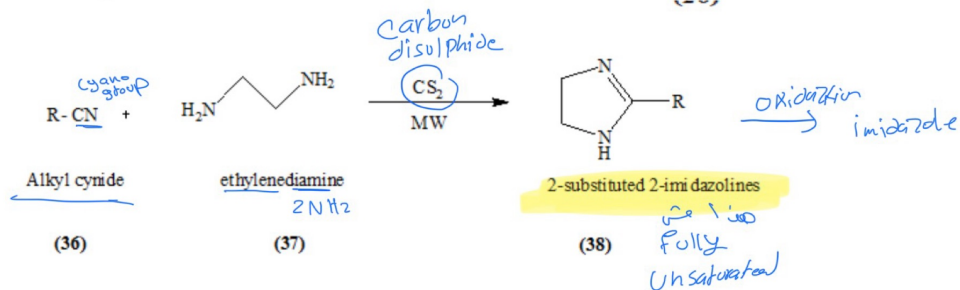
Benzil (dicarbonyl compound) + 2 mol NH_3 + benzaldehyde / Ketoaldehyde / diketone $\rightarrow$ 2,4,5-triphenylimidazole

③ Wallach $\Rightarrow$ sulf le ions
 Imidazole containing
 chlorine (Cl)

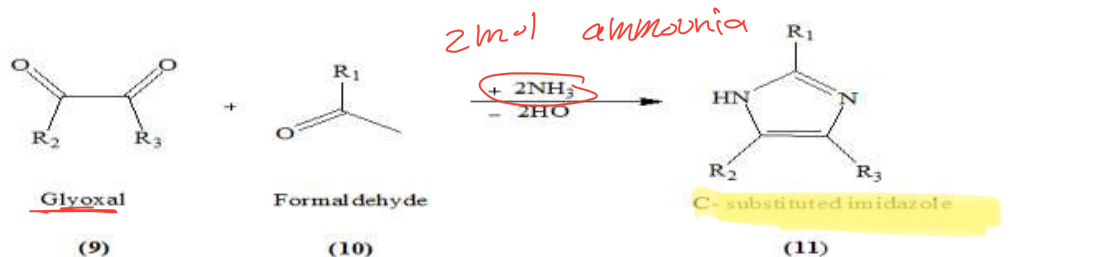
N,N -dimethyl oxamide + PCl₅ $\rightarrow$ Chlorine
 containing
 compound
 (oxidizing
 agent)
 $\downarrow$ HI
 (reduction)
 N,N -methyl imidazole

N,N -diethyl oxamide + PCl₅
 $\downarrow$
 chlorine containing compound
 $\downarrow$ HI (reduction)
 1-ethyl-2-methyl imidazole

④ microwave :



مركبة ينتج كمية قليلة جداً
(low yield)

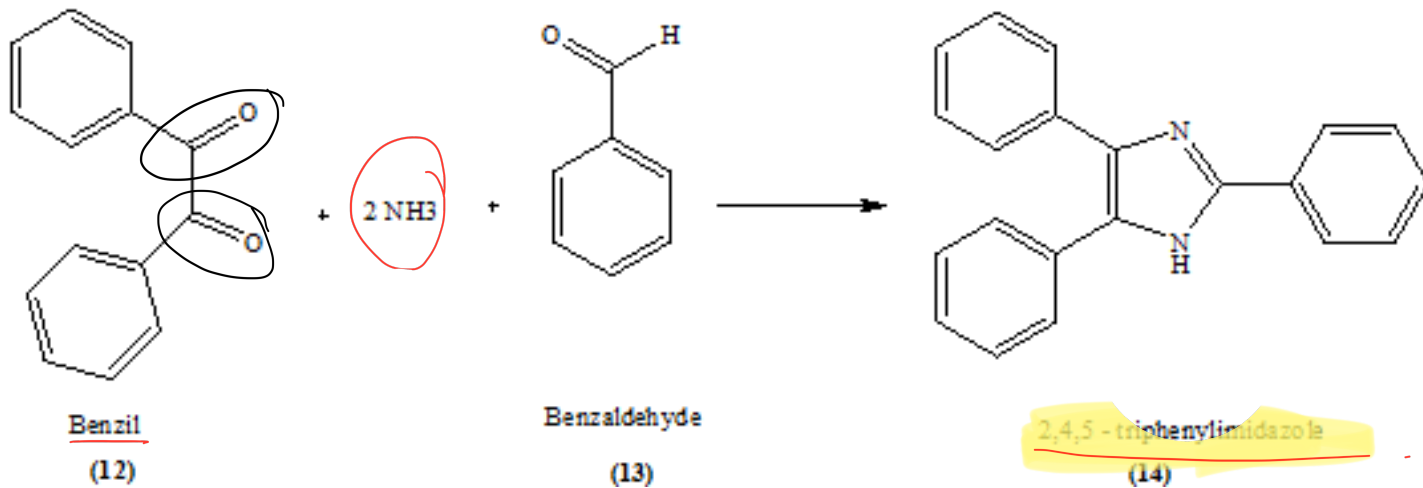


1) Debus Synthesis:-

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]

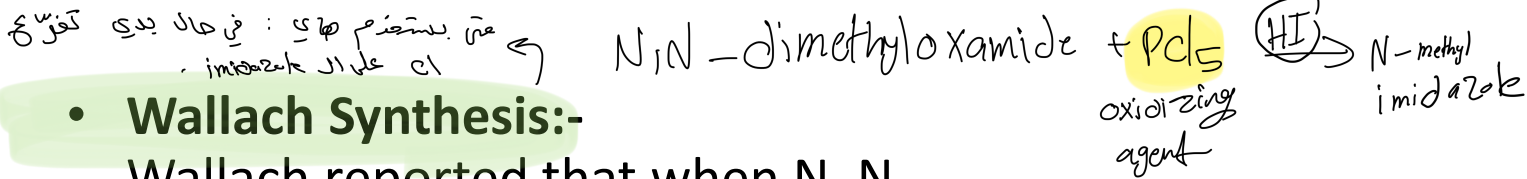
2) Radiszewski Synthesis:

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



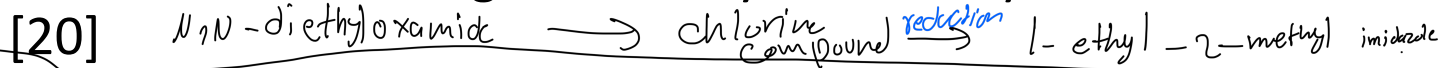
dicarbonyl compound (Benzil) + 2 mol of NH_3 + keto aldehyde or benzaldehyde or di ketone $\longrightarrow$ 2,4,5 - triphenyl imidazole

$\Rightarrow$ Radiszewski

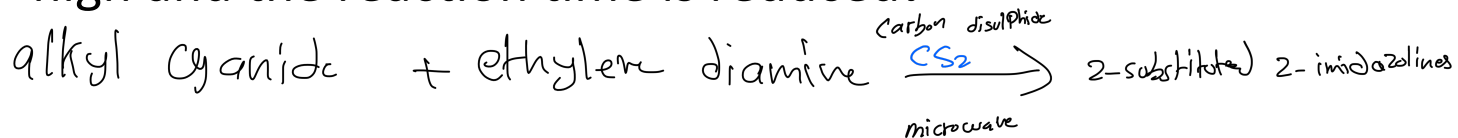


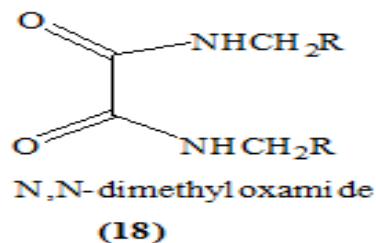
• Wallach Synthesis:-

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.



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.



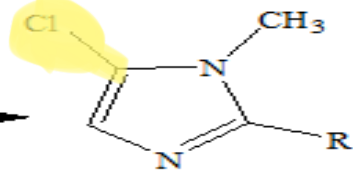


+

PCl5

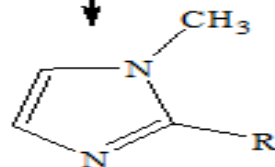
oxidizing agent

oxidation

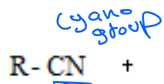


Chlorine containing compound
(19)

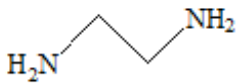
reduction $\downarrow$ HI hydroiodic acid



N-methyl imidazole
(20)

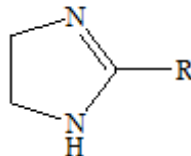


+



carbon disulphide

CS_2
MW



2-substituted 2-imidazolines

(38)

oxidation $\rightarrow$ imidazole

is also fully unsaturated

Alkyl cyanide

(36)

ethylenediamine
 2NH_2

(37)

Reactivity of the Imidazole Ring

فعلية Nitrogen alkyl group على ال Nitrogen

alkyl group

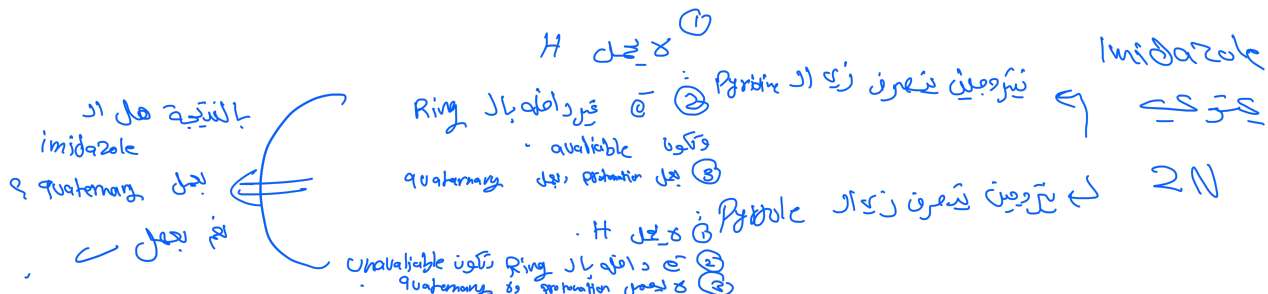
SN2

imazole : SN2 (prime)

• Nitrogen Alkylation

- Alkylation of the nitrogen occurs readily and is either via direct SN2 or SN2⁽¹⁾, 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.

① Basicity : قاعدية الوسط
② electrophile : نوع ال electrophile
③ steric hindrance : ال steric hindrance



Electrophilic C-Substitution

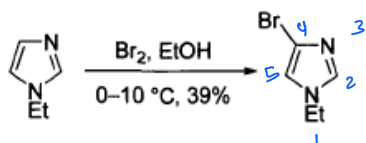
Reactions of the imidazole carbon atoms occur easily under basic or neutral conditions; however, once protonated, electrophilic substitution is slowed.

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

نمو الملمم جالس يد:

① rxn of imidazole
يتكون أنسجل في وسط قاعدي أو متعادل

عند هذه الحلقة يتكون الكتر دنا في فتحة ديسر
اتفاعل بشكل أنسجل أما بالوسط الحمضي يتكون الحلقة
مقصر بالة كدروا ح .



imidazole
علة استبدال H
بال Ethyl group
عشان أنسجل حلقه

فيين حار ان
Bromination of imidazole

④ على position رقم

قواعد الترتيب:

① N > S > O

② اذا كان

N و NH
فقد آمن NH .

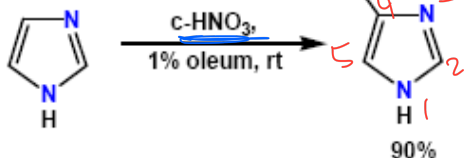
② إضافة electrophile من إضافة halogen
nitr group
يكون آمن امسي على مواقع 4 و 5
وانتم بيلت فن
N على متبوعه بار H .

1,3-Azoles – Electrophilic Substitution

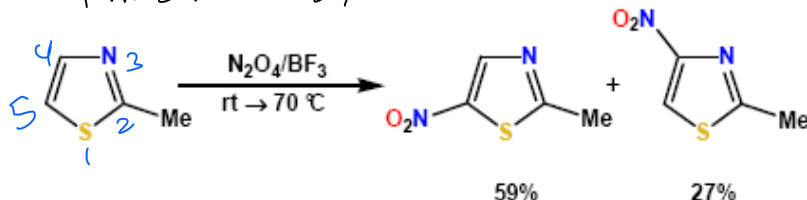
أول
No2

Nitration

Imidazole: 4-position



Thiazole: 5-position



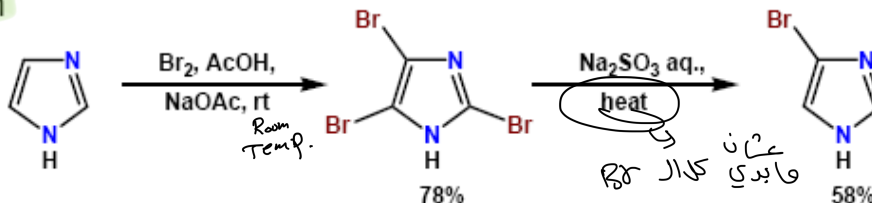
- Imidazoles are much more reactive to nitration than thiazoles (activation helps)
- Imidazoles usually nitrate at the 4-position and thiazoles tend to react at the 5-position
- Oxazoles do not generally undergo nitration

(O, N)

(S, N)

oxazole / thiazole / imidazole
: nitration يسهل على
Imidazole > thiazole > oxazole

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

Imidazoles

bromination 11 مرة
عنه 80%

> Thiazoles

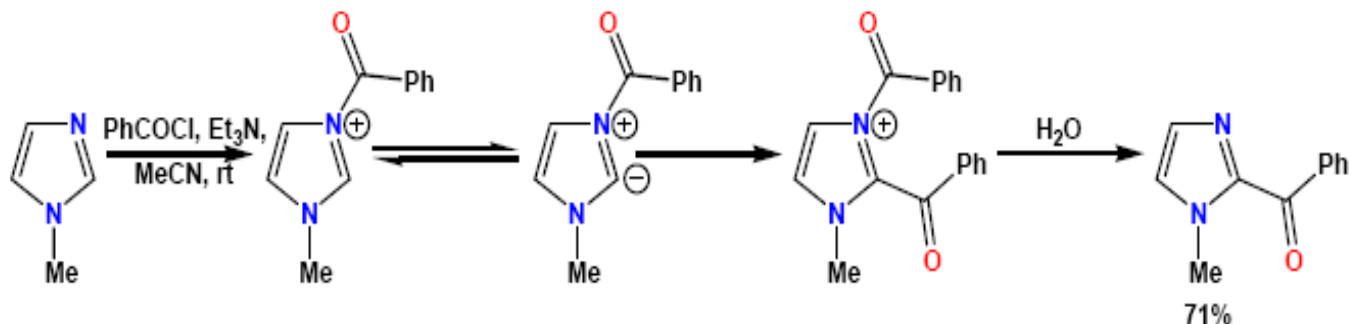
2-alkylthiazole
(5) يسهل bromination له

فهو

السر

Bromination

Acylation



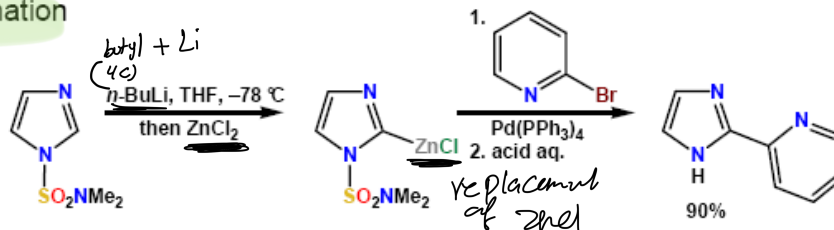
- 1,3-Azoles do not undergo Friedel-Crafts acylation because complexation between the Lewis acidic catalyst and *N* deactivates the ring.
- Acylation can be accomplished under mild conditions *via* the *N*-acylimidazolium ylide

1,3-Azoles – Metallation

well known electrophilic substitution rxn.

Direct Deprotonation

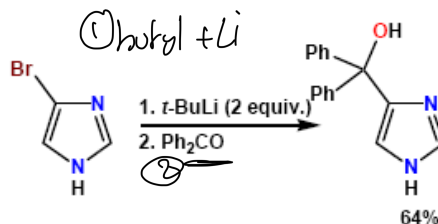
نزع H
Li = lithium



- 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

بدون نزع H و بدون Li
حاصل از halogen بر Br و بدون
نیست و Li



- 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

N-H imidazole needs 2 BuLi