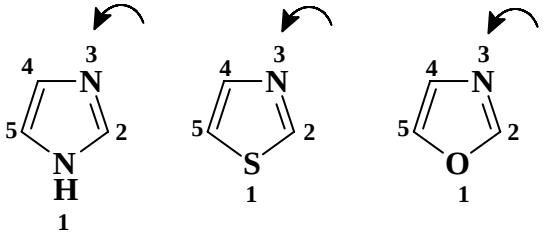
PENTAHETARENES WITH TWO HETEROATOMS IN POSITIONS 1, 3

Modifications (improvements, additions, corrections, up to dates *etc.*) are subjected to no notice.

HETARENE PENTAATOMICE CU DOI HETEROATOMI IN POZITIILE 1,3

1. Generalitati:

a) reprezentanti tipici:



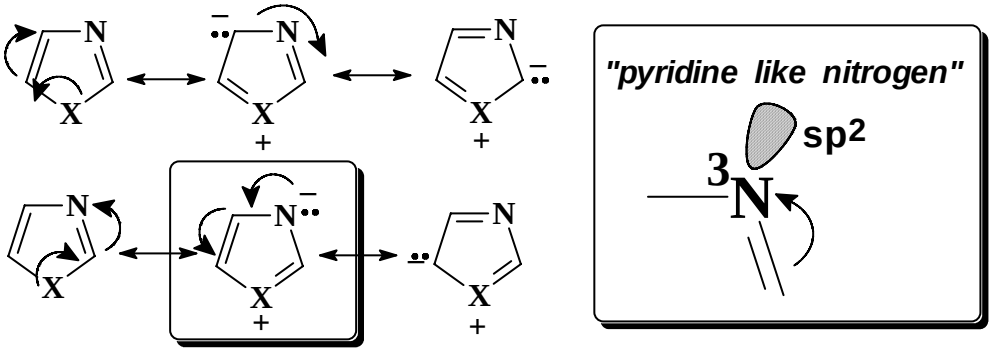
1,3-diazOL imidazol | **1,3-tiazOL tiazol** | **1,3-oxazOL oxazol**

P r i o r i t a t i de citare (I U P A C):

O (oxa) > S (tia) > N (aza) >P (fosfa) > As (arsa)

Daca **mai multi heteroatomi diferiti** se gasesc intr-un ciclu, **pozitia heteroatomului cu prioritate de citare mai mare** se numeroteaza **1**; **ceilalti heteroatomi** primesc **cele mai mici numere posibile.**

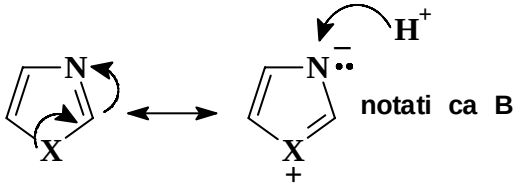
b) caracterul aromatic: caracter aromatic in general **mai accentuat** decat analogii cu **un singur** heteroatom



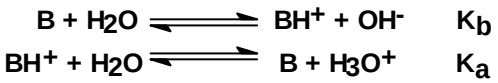
- *N*-3: centru nucleofil preferat de electrofili
- centru protonabil
- aza - atomul "piridinic" accentueaza caracterul aromatic
- scade afinitatea -*C*H= fata de electrofili
- creste afinitatea -C*H*= fata de baze si nucleofili

Observatie utila: *1,3-azolii pot fi considerati ca "hibrizi" intre (furan, tiofen, pirol) si piridina.*

c) caracterul acido – bazic:

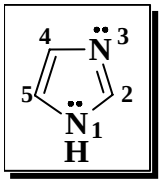


notati ca B

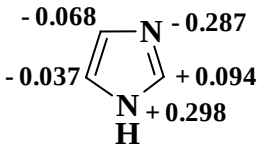


X	NH	S	O	
pK_b	7.0	11.5	13.2	referitor la B
pK_a	7.0	2.5	0.8	referitor la BH^+

Nota : *N*-3 este un centru a carui **bazicitate** depinde: **a)** de **disponibilitatea conjugativa** a heteroatomului **X** (ca electronegativitate); **b)** de **stabilitatea acidului** rezultat (a formei protonate)

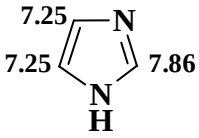


imidazole as neutral form



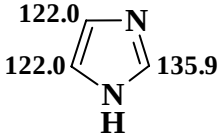
π –charges

^{1}H-NMR

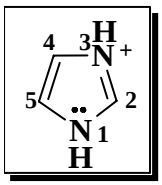


δ –values (ppm)

^{13}C-NMR

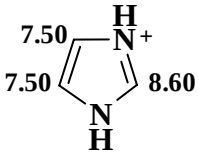


δ –values (ppm)

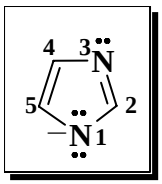


imidazolium cation

^{1}H-NMR

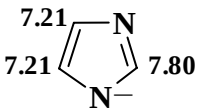


δ –values (ppm)

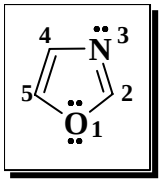


imidazolium anion

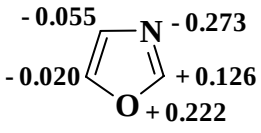
^{1}H-NMR



δ –values (ppm)

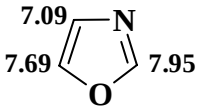


oxazole



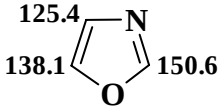
π –charges

^{1}H-NMR

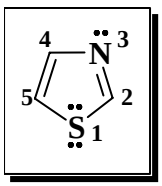


δ –values (ppm)

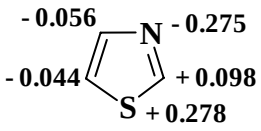
^{13}C-NMR



δ –values (ppm)

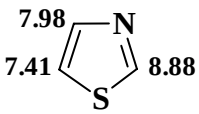


thiazole as neutral form



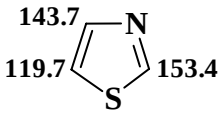
π –charges

^{1}H-NMR

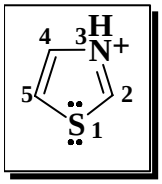


δ –values (ppm)

^{13}C-NMR

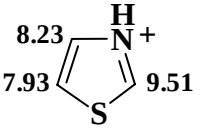


δ –values (ppm)



thiazolium cation

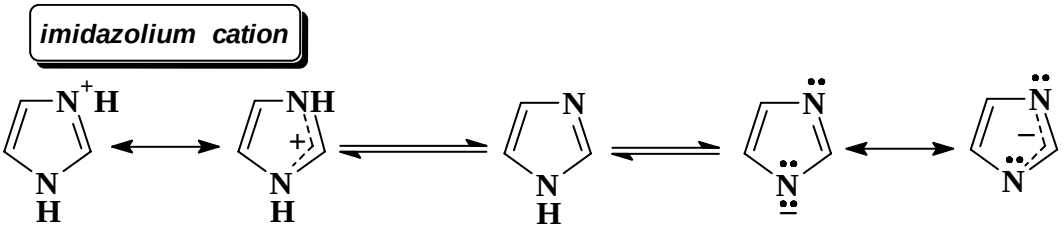
^{1}H-NMR



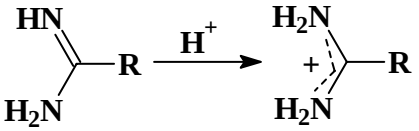
δ –values (ppm)

As a rule for positions with *negative π – charges*, the corresponding signals move towards *higher field* (shielding) with respect to benzene, whereas shifts towards *lower field* (deshielding) are observed for nuclei carrying *positive charges*

c) imidazolul ca amfolit:



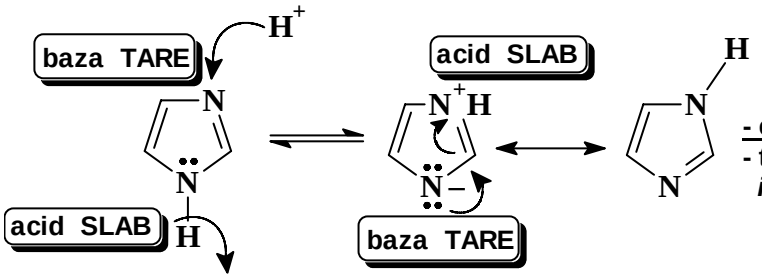
similar cu:



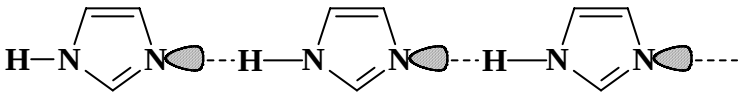
cation amidiniu

(daca *N*-3 devine -CH=
pKa = 16.5 pKb = - 2.5)

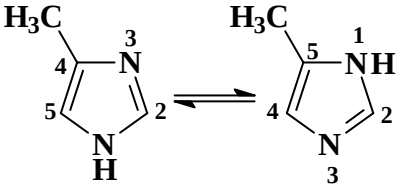
d) tautomeria imidazolilor:



- echilibru rapid pe scala de timp IR si RMN
- tautomerie prototropica atat *intra* cat si *inter*-moleculara (date IR)



- asociate moleculare in stare lichida si in solutie (oligomeri)
- solid (p.t. = 90°C, p.f. = 256°C)
- momentul dipolar global (D): μ = 6.2

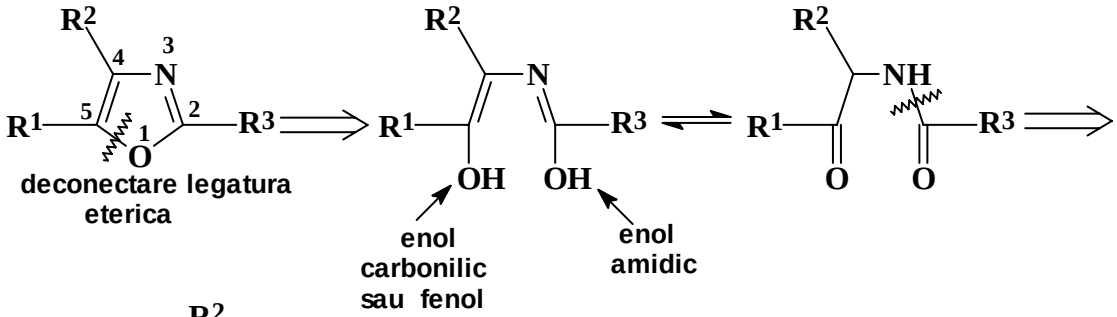


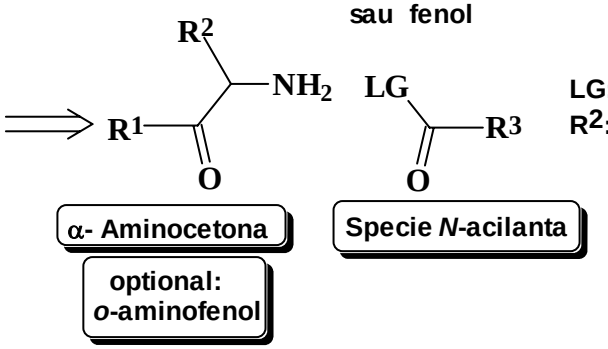
- nediferentiabili prin UV, IR, ^{1}H-RMN
- denumirea 4(5)-metilimidazol

2. Sinteze:

2.1. 1,3 – Oxazoli, varianta Gabriel & Robinson

- retrosinteza: deconectare hidrolitica (1-5 sau 1-2) apoi (2-3)

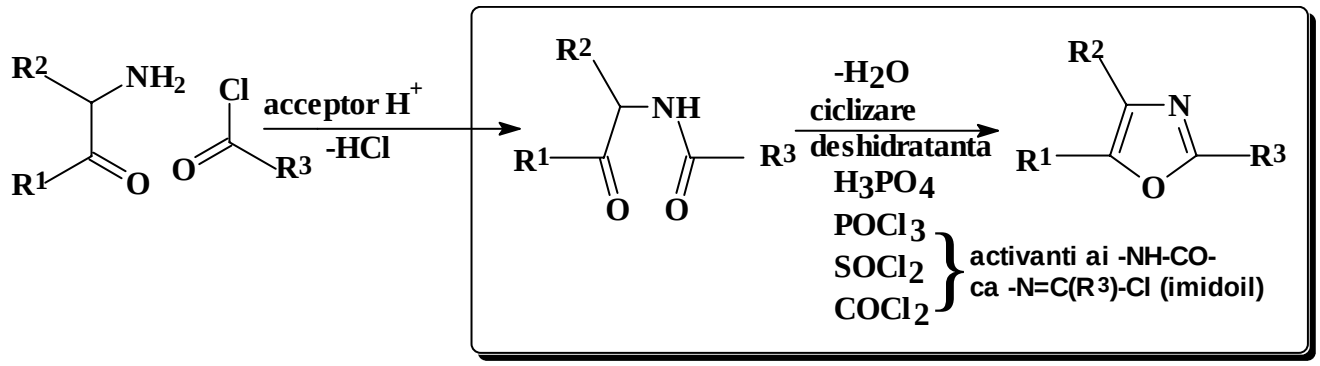




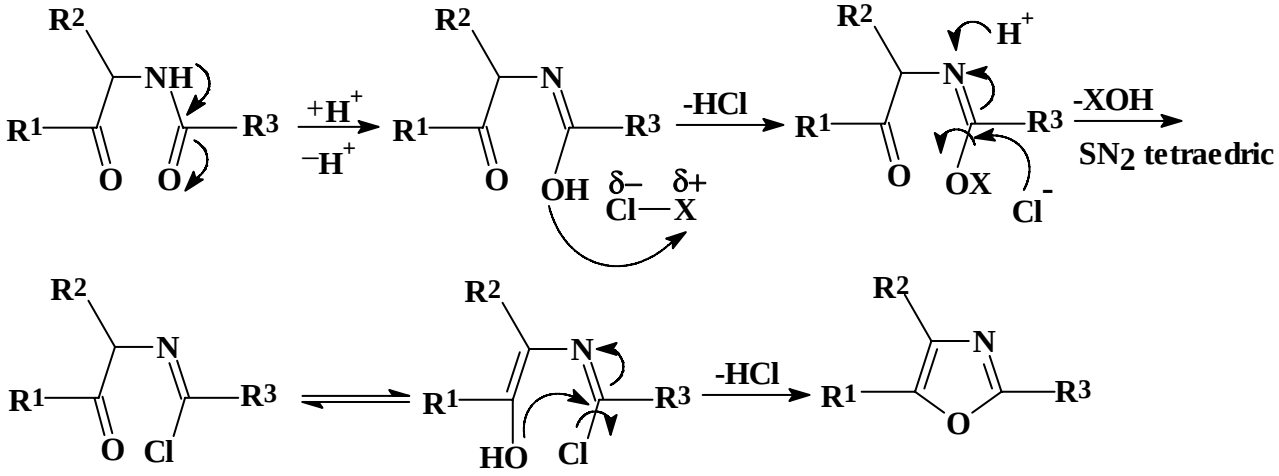
LG: Cl, RO- inferior, OH

R2: efectul electronoatragator nu este o cerinta primordiala

- **sinteza:**

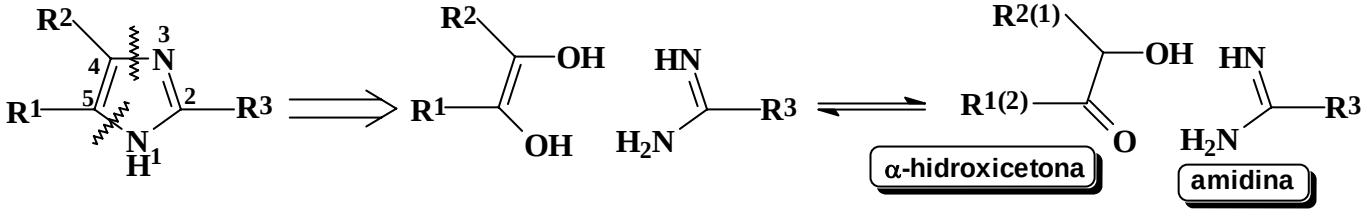


$POCl_3, SOCl_2, COCl_2 = X^{\delta+}-Cl^{\delta-}$ (X: $O=PCl_2$, $O=SCl$, $O=CCl$)

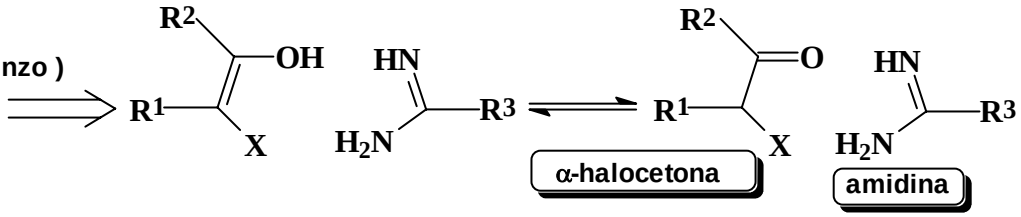


2.2. Metode generale de preparare a imidazolilor:

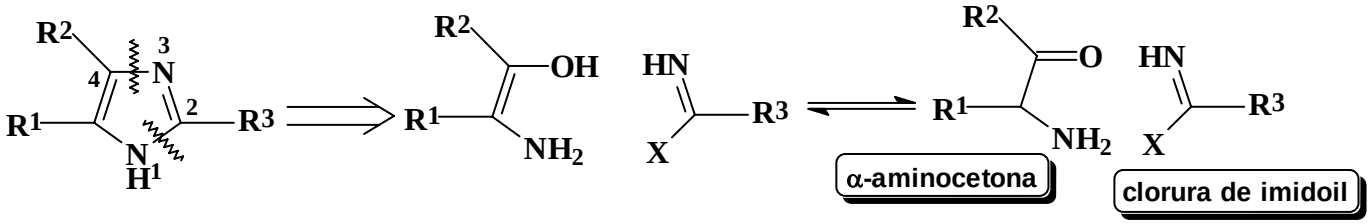
-deconectare hidrolitica in tautomerul 1*H* : (3-4)-(1-5)



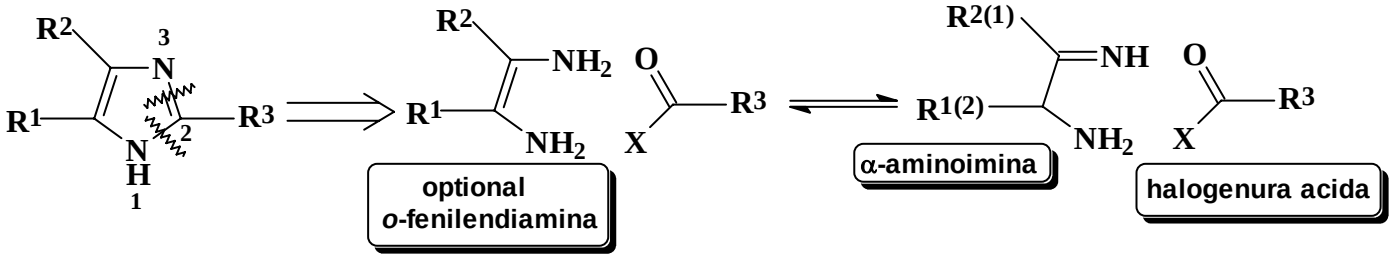
optional
(R1, R2 nu sunt benzo)



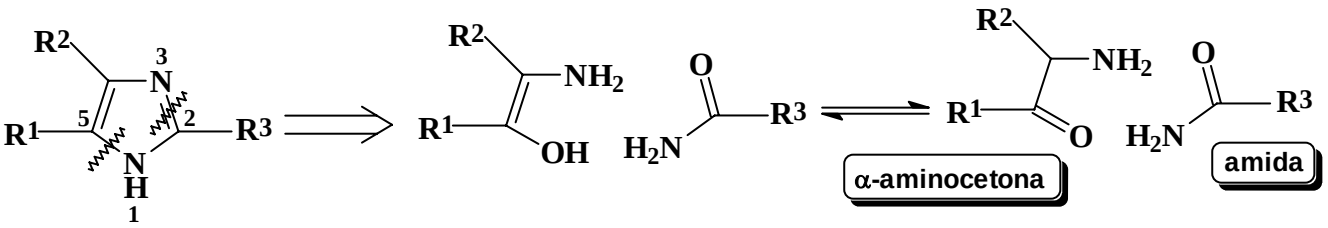
- **deconectare hidrolitica in tautomerul 1*H*: (1-2)- (3-4)**



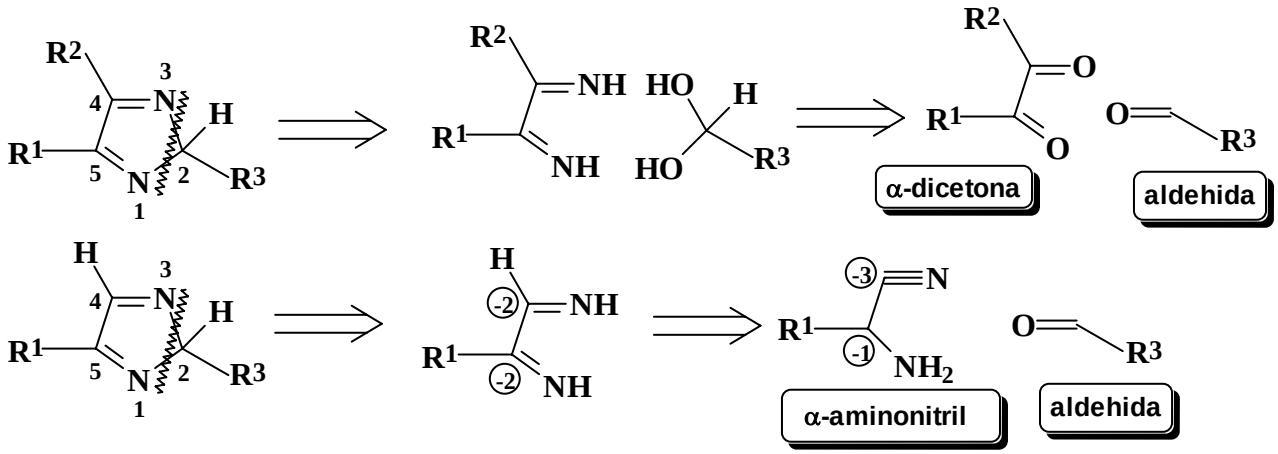
- **deconectare hidrolitica in tautomerul 1*H*: (1-2)- (2-3)**



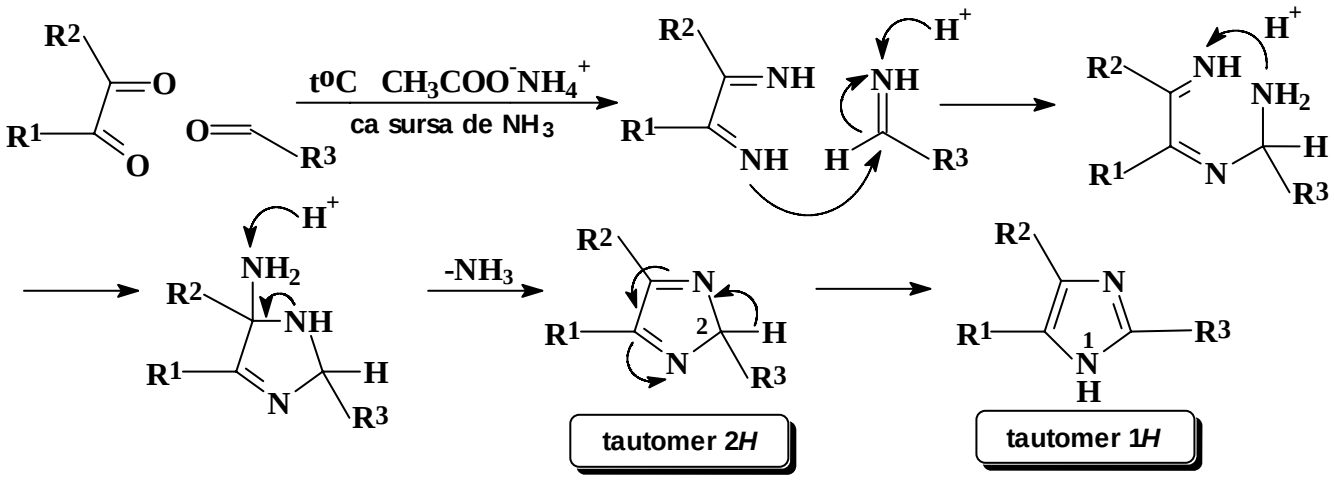
- **deconectare hidrolitica in tautomerul 1*H*: (2-3)- (1-5)**



- **deconectare hidrolitica in tautomerul 2*H*: (1-2)- (2-3) echivalenta cu (3-4)- (1-5)**



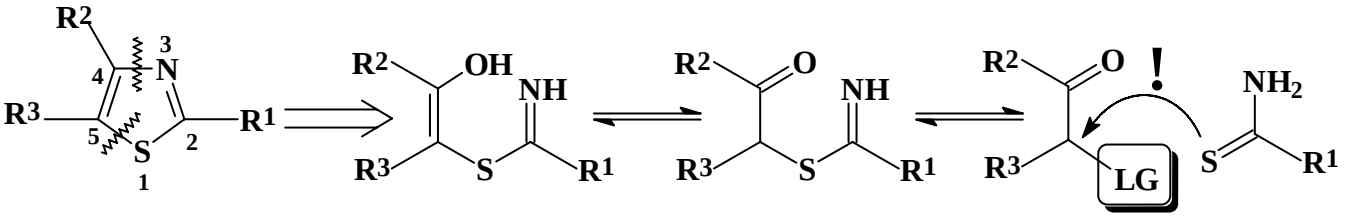
Nota 1: nu exista “metoda preferata” de sinteza
Nota 2: pentru benzimidazoli, deconectarea ca **1*H* (1-2)- (2-3)** este cea mai avantajoasa
Nota 3: metoda cea mai simpla si uzuala utilizeaza **α-dicetone** si o **aldehida** in prezenta amoniacului **(cazul cel mai simplu: $R^1 = R^2 = R^3 = H$,** rezulta **imidazolul ca atare)**



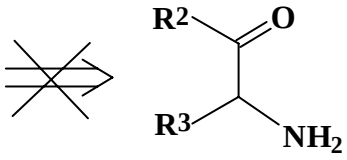
Nota 4: sunt accesibili, pe aceste cai, imidazoli **exhaustiv *C*-substituiti**
Nota 5: tautomerii **1*H*** **($R^1 \neq R^2 \neq R^3$) si 3*H*** **($R^1 \neq R^2 \neq R^3$)** sunt **regioizomeri nediferentiabili**

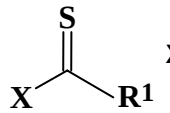
2.3. Sinteza tiazolilor

- **retrosinteza: deconectare hidrolitica (3,4)-(5-1) varianta "clasica" Hantzsch (1888)**



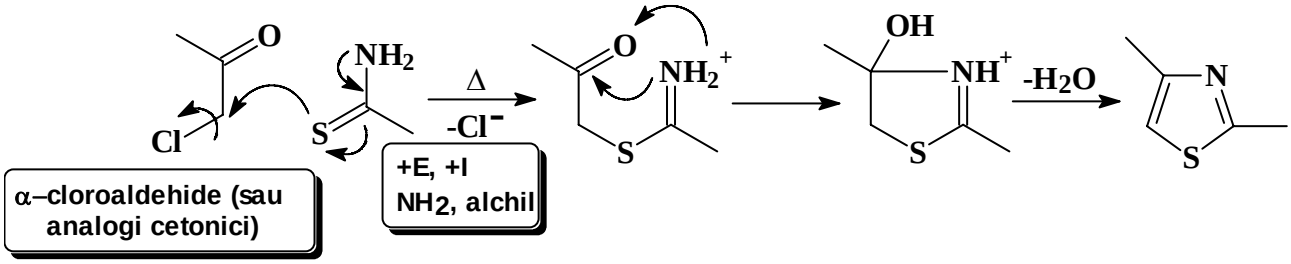
LG: de tip **halo (Cl, Br, I), usor polarizabil**
R1: electronodonor (*e.g.* NH_2)



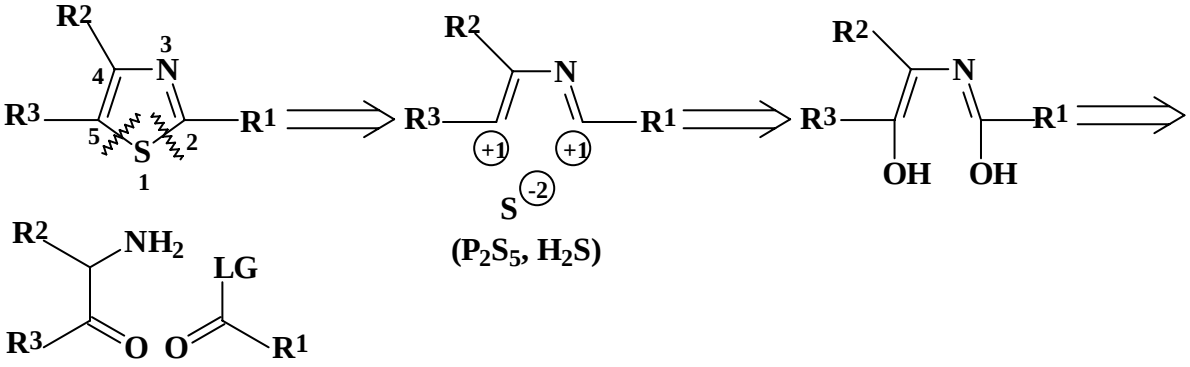


greu accesibile si instabile

Exemplu:

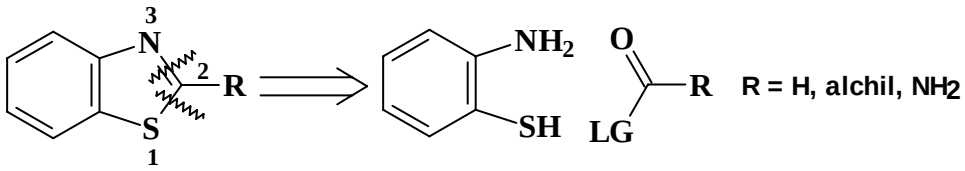


-deconectarea (1,5)-(1,2)-(2-3) (varianta redox este mai avantajoasa)



(P_2S_5, H_2S)

- deconectare hidrolitica (1,2)-(2-3) in seria benzotiazolilor

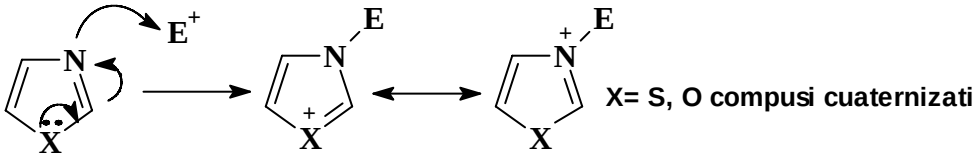


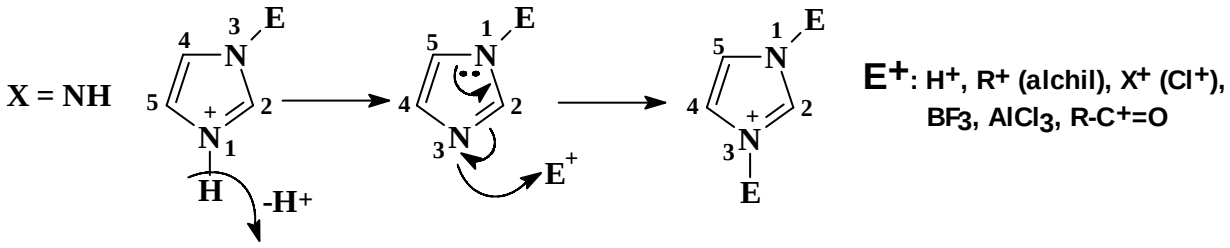
R = H, alchil, NH_2

3. Functionalizarea:

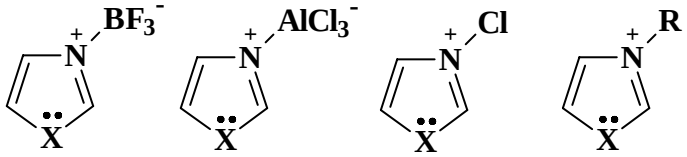
3.1. Functionalizarea prin SE:

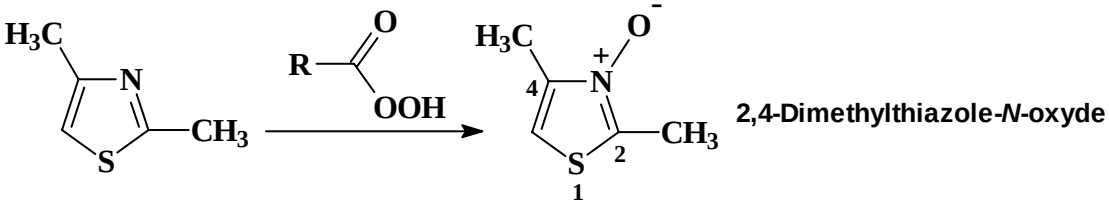
3.1.1. Functionalizarea prin SE la *N*-piridinc:



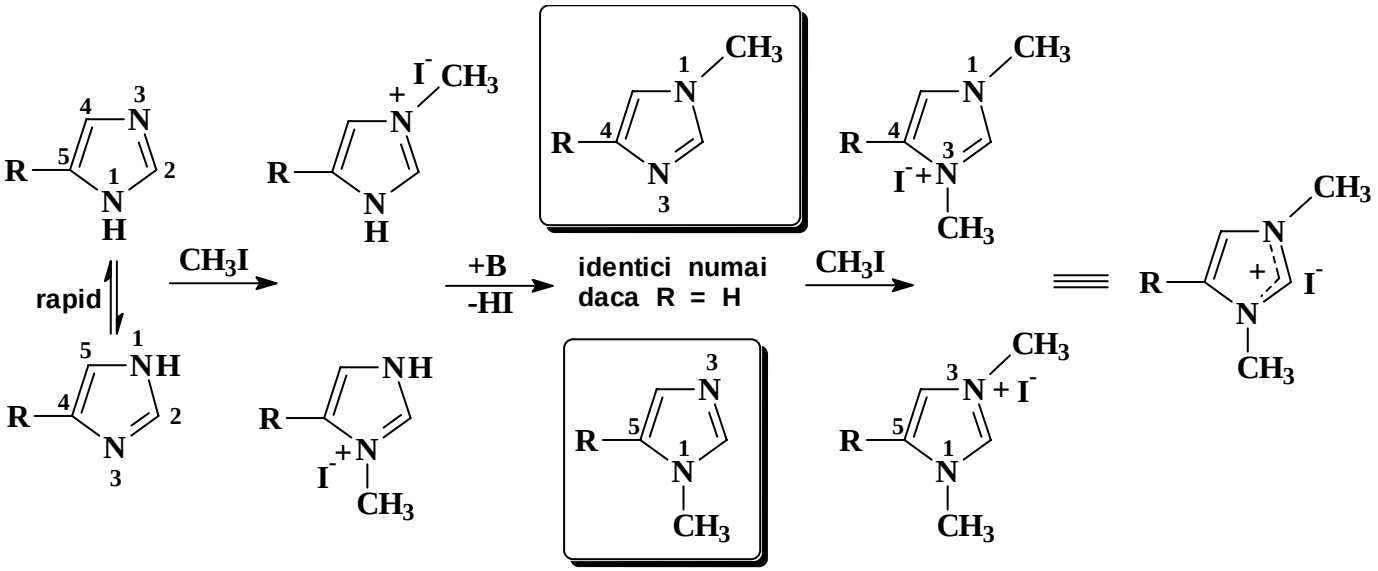


Exemple:



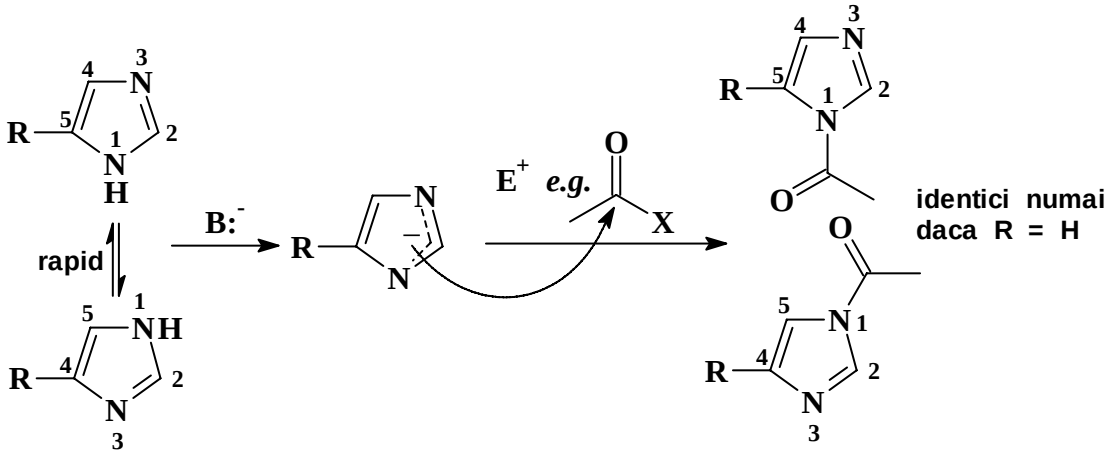


- **tautomerii imidazolului:** pot fi discriminati in cazul ***monosubstitutiei*** pe un substrat de pornire ***nesimetric*** substituit

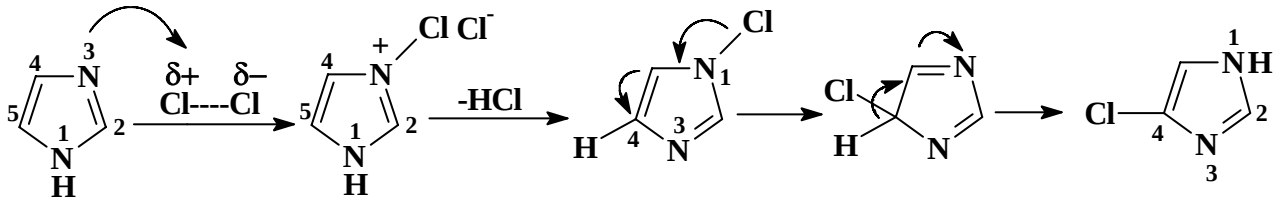


Nota 1: in mediu neutru sau acid, functionalizarea prin SE are loc totdeauna la azotul piridinic (*N*-3)
Nota 2: protonul **H$^+$** precede orice alt electrofil (eventual prezent): ***N*-3** este, in **primul rand bazic** si **apoi** nucleofil

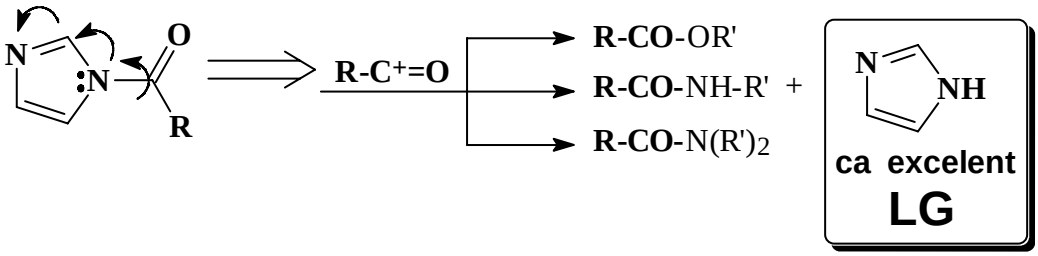
- **in mediu alcalin, prioritatea azotului piridinic dispare:**

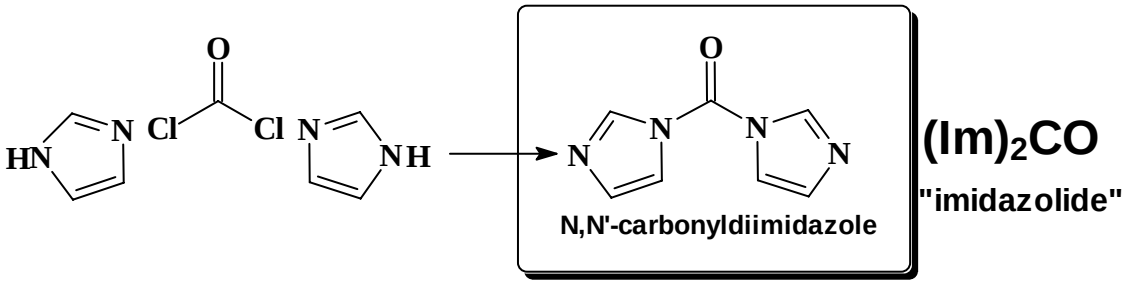


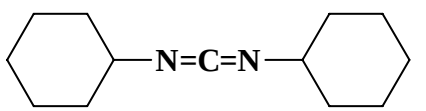
- **concurenta *N- vs. C*-substitutie:**



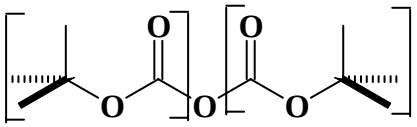
- ***N*-acilimidazolii ca agenti de *O*- si *N*-acilare:**



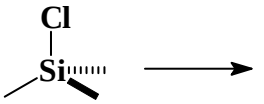




Dicyclohexylcarbodiimide **DCC**



tert-Butoxycarbonyl anhydride **(Boc)$_2$O**

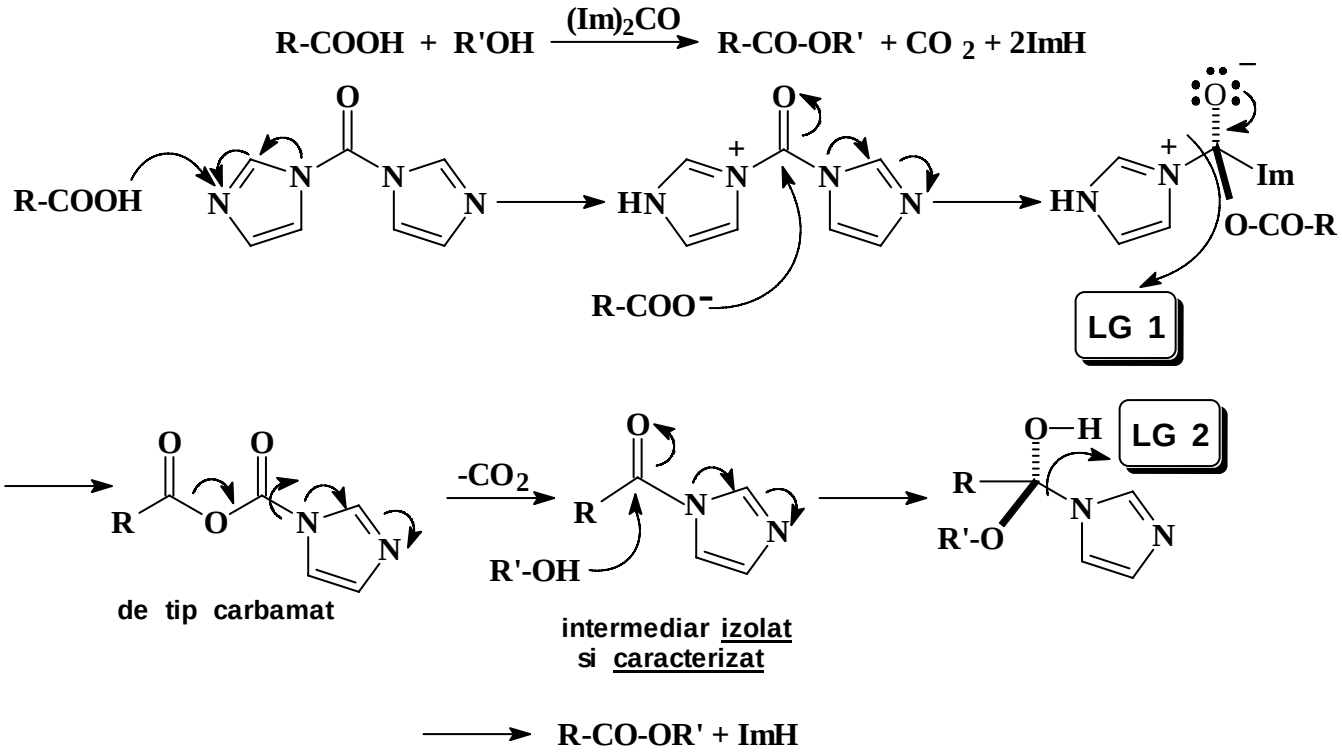


$(Me)_3Si^+$ "fat proton"

TriMethyl Silyl chloride **TMSCl**

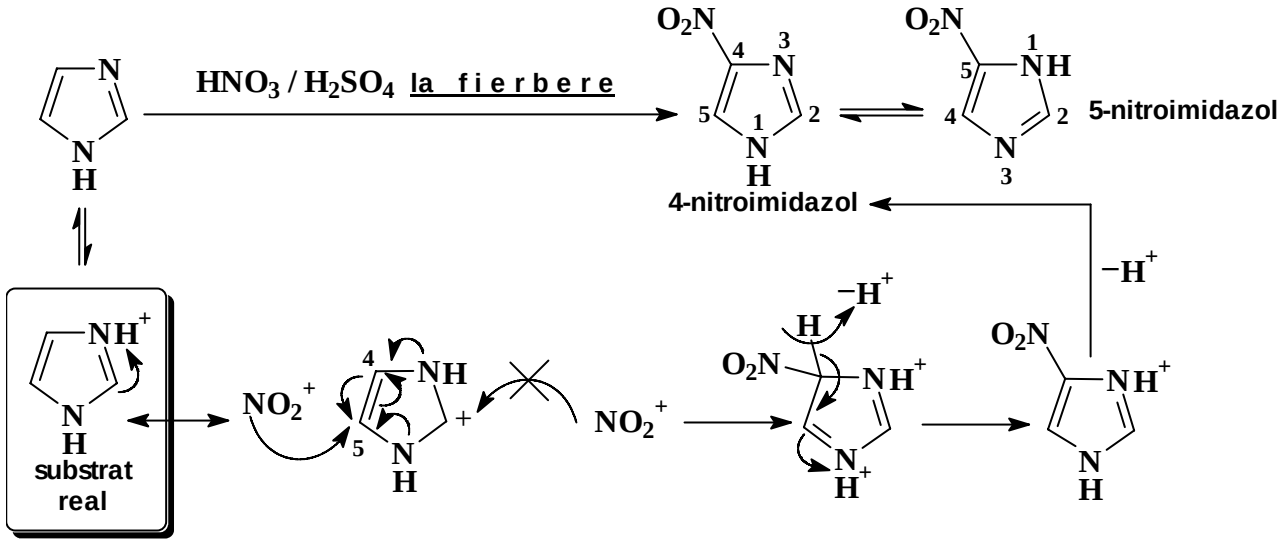
caracteristici: acilanti, deshidratanti, excelenti LG → **B l a n z i**

- **exemplu:** esterificarea **mediata** de **$(Im)_2CO$** ca succesiune de doua mecanisme tetraedrice

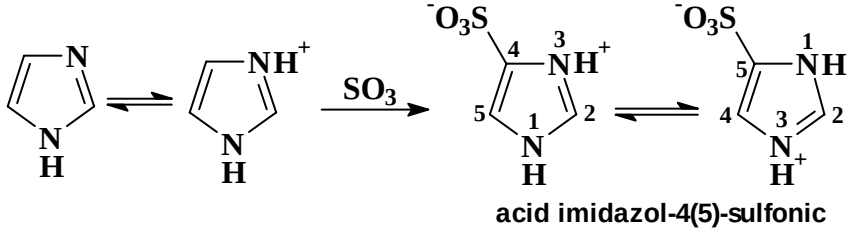


3.1.2. *C* - functionalizarea prin SE:

a) nitrarea: conditii extrem de energice



b) sulfonarea: la 160°C cu SO_3 / H_2SO_4 la 150 – 200°C

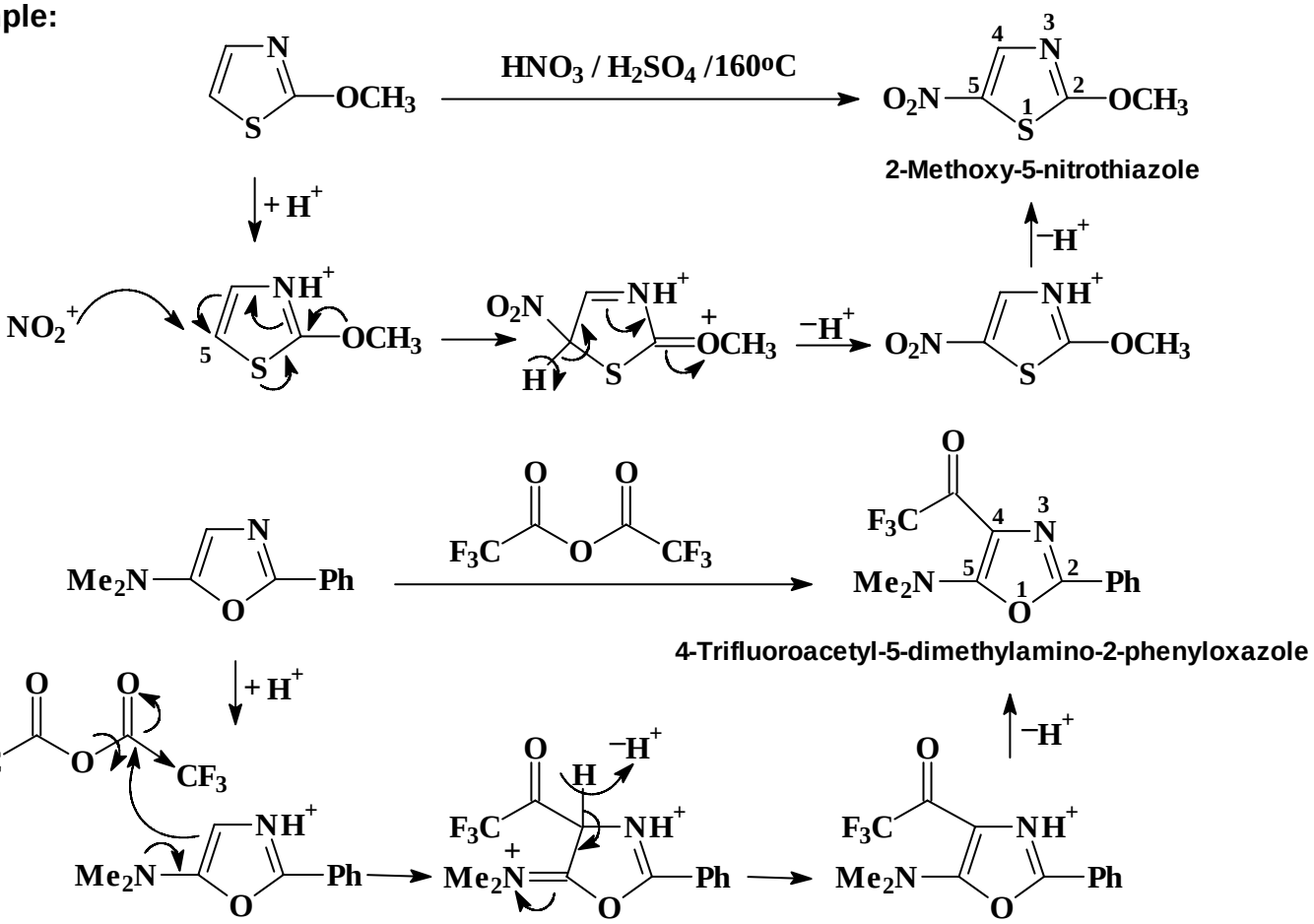


Nota: substitutia electrofila la **–*C*H= nu** are loc niciodata la **C-2.**

c) substitutia electrofila la –*C*H= poate fi **oarecum facilitata** daca:

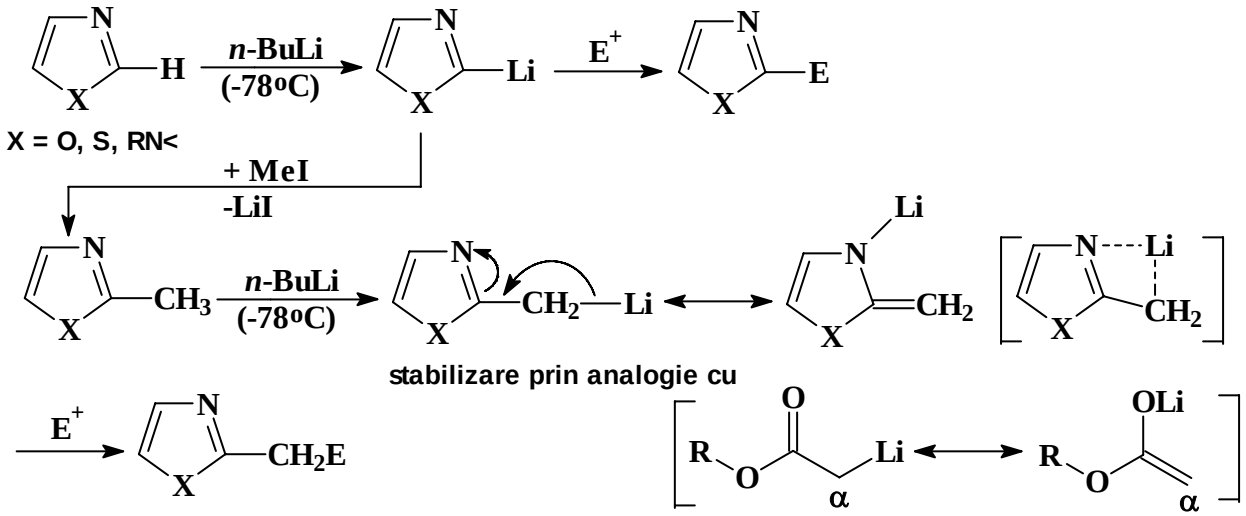
- este prezent la **C-2** (si **C-5**) un **presubstituent puternic activant (+E) care insa mareste si bazicitatea la *N*-piridinic**
- este prezent un **electrofil dur**
- conditiile de reactie raman **dure**

Exemple:



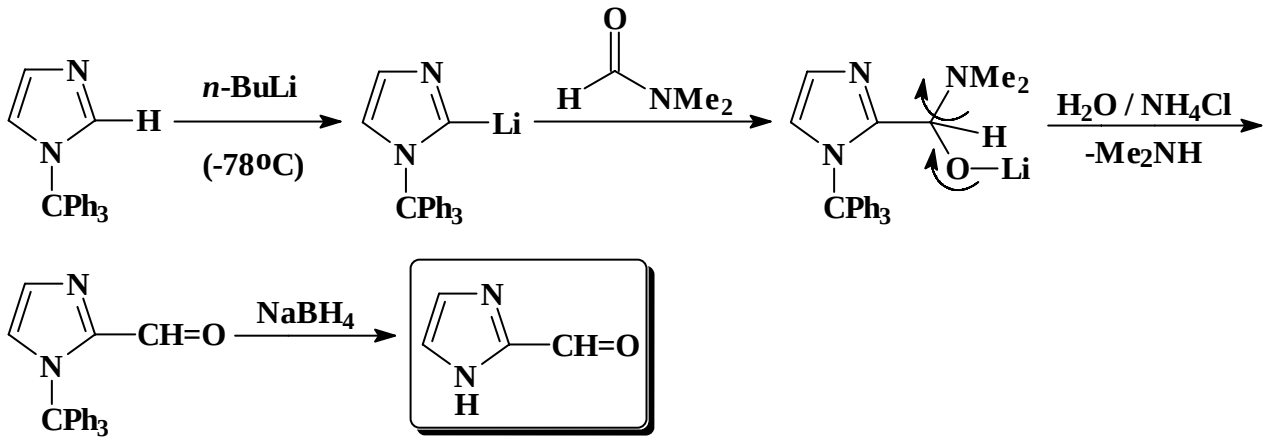
3.1.3. Functionalizarea prin SE *via* metalare

- **are loc la C-2**
- o grupare **metil** atasata la **C-2 este deprotonabila**

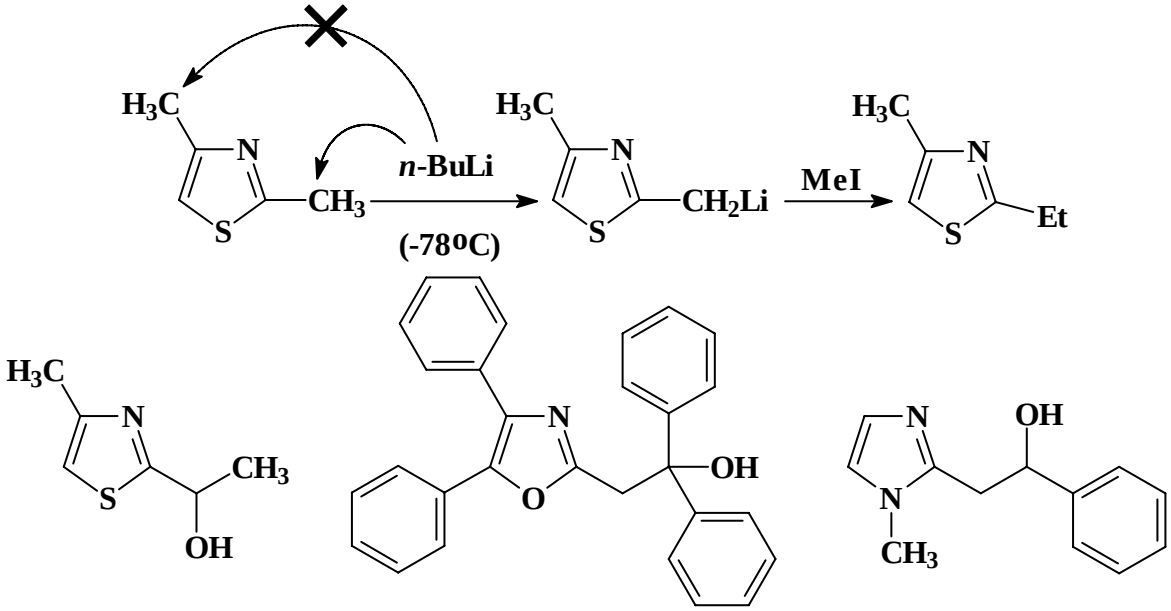


Exemple:

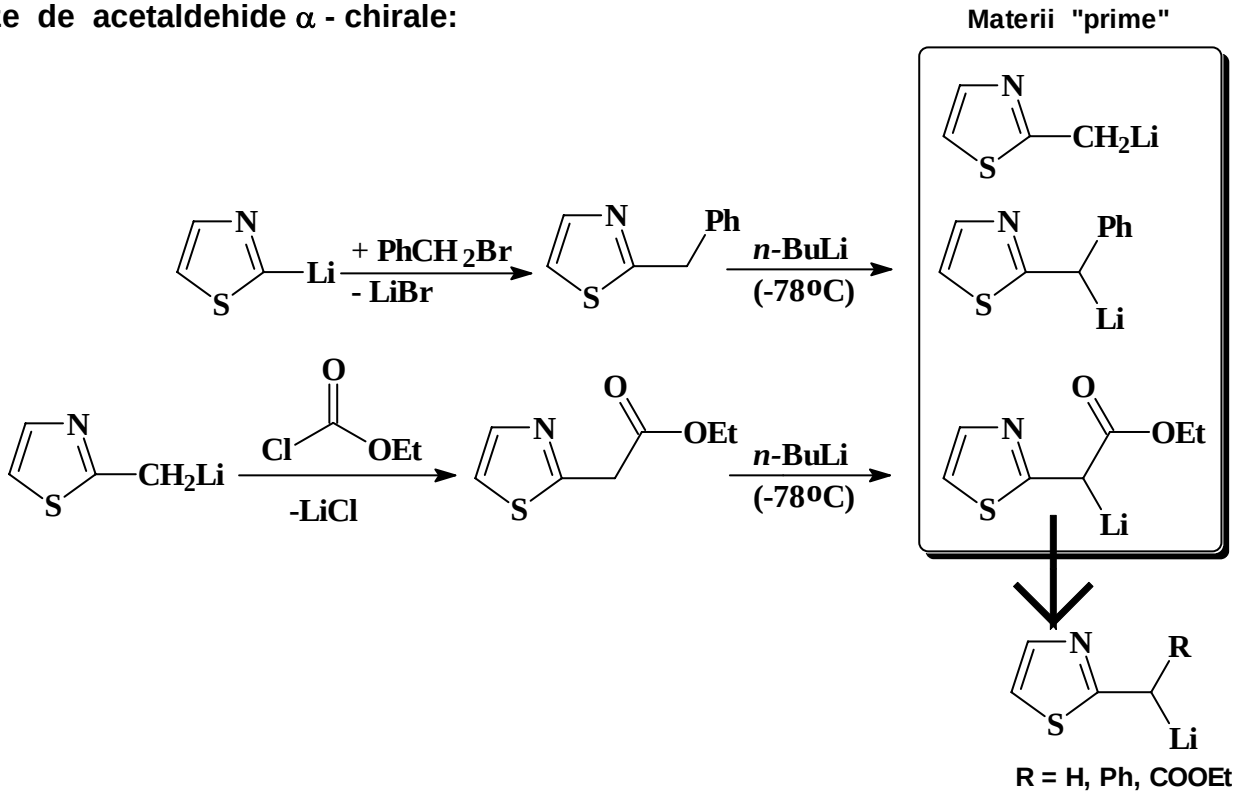
- formilarea la C-2 imidazolului:

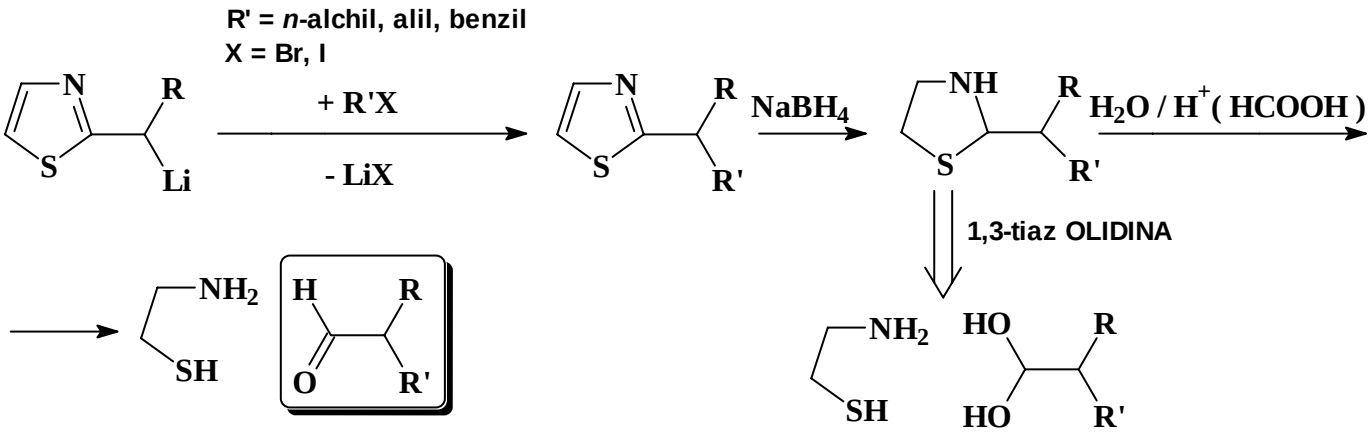


- metalare **regioselectiva:**



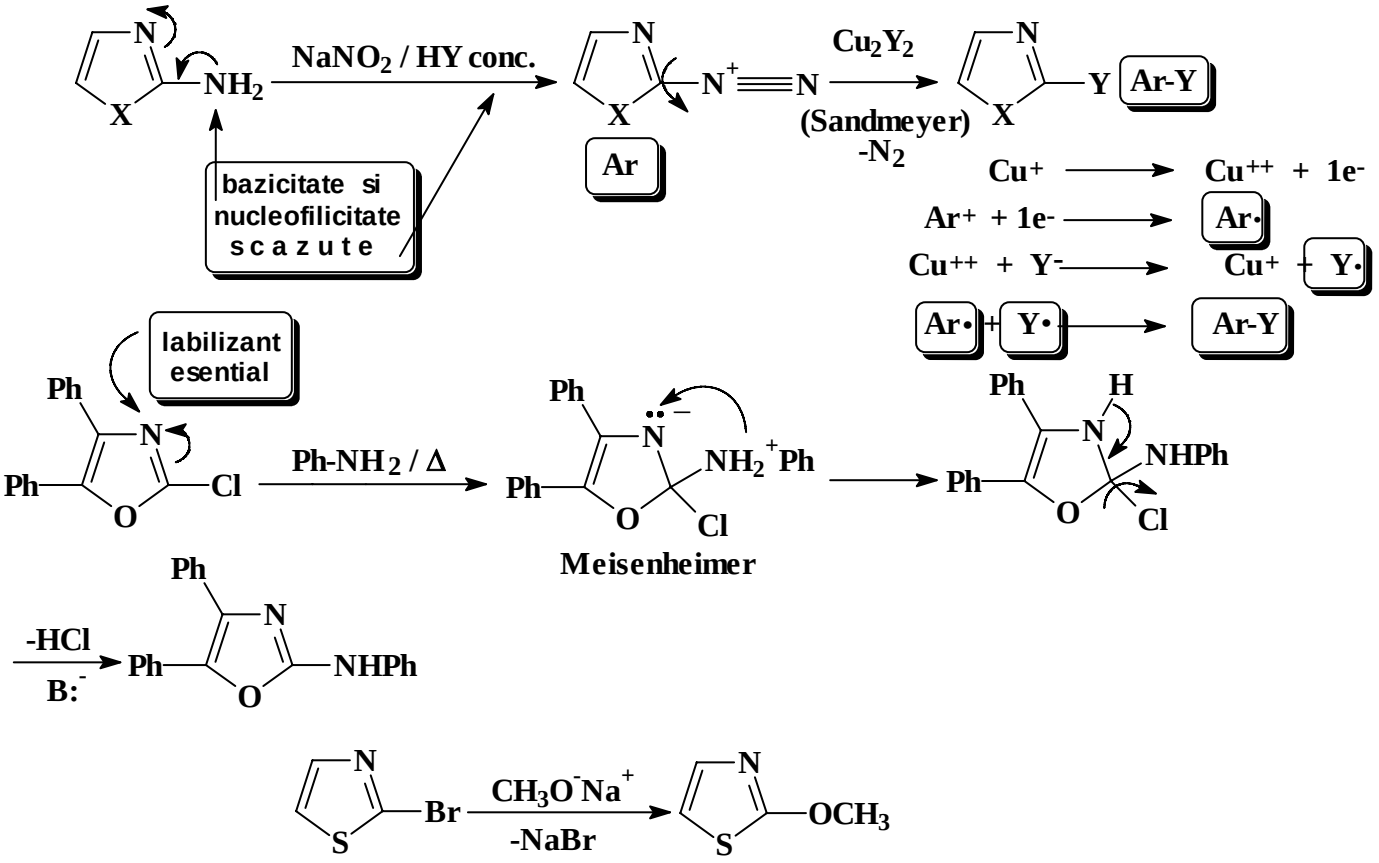
- sinteze de acetaldehide α - chirale:





3.2. Functionalizarea prin substitutie nucleofila

a) substraturi 2-halo substituite: *N*-piridinic ca **labilizant**



b) cuplarea a doua unitati pentaheterociclice: