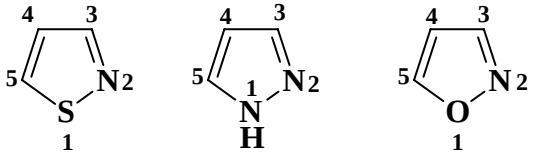
PENTAHETARENES WITH TWO HETEROATOMS IN POSITIONS 1, 2

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

HETARENE PENTAATOMICE CU DOI HETEROATOMI IN POZITIILE 1,2

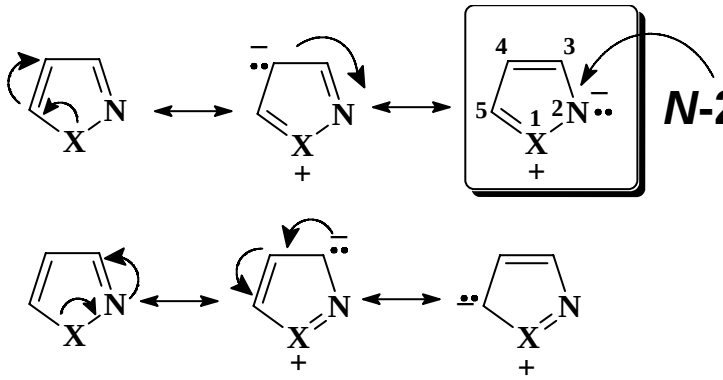
1. Generalitati:

a) reprezentanti tipici: 1,2 - azolii



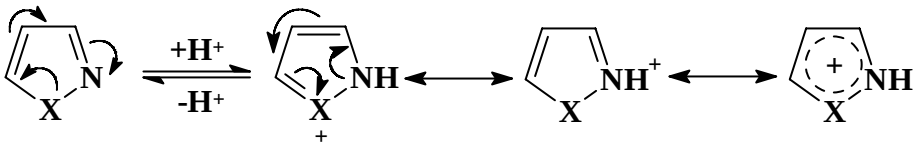
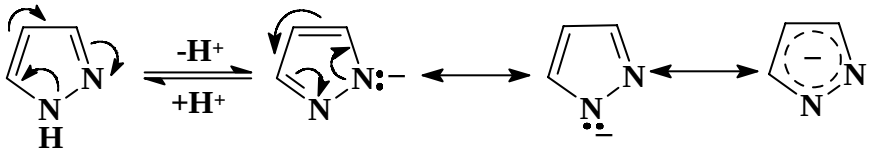
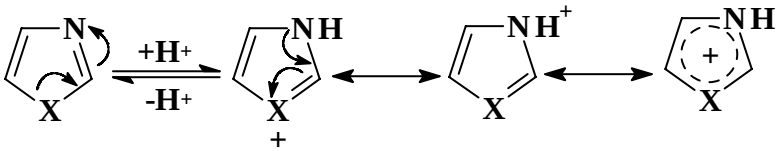
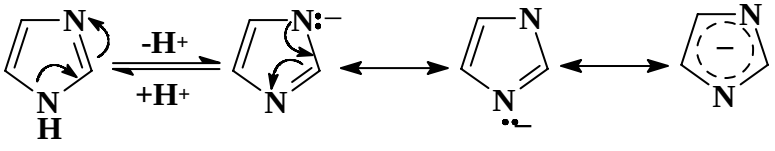
1,2-tiazOL *izo*tiazol | 1,2-diazOL pirazol | 1,2-oxazOL *izo*xazol

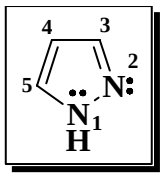
b) caracterul aromatic: caracter aromatic in general **mai scazut** decat analogii **1,3 - azoli: S > NH > O.**



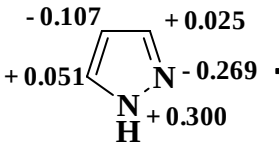
***N*-2:** aza-atom "piridinic" cu bazicitate si nucleofilicitate diminuate fata de analogul ***N*-3** din 1,3-azoli datorita vecinatatii dezactivante (efect- I_X) a heteroatomului **X** **(O > S > N)**

c) caracterul acido – bazic: **bazicitate sensibil mai scazuta decat analogii 1,3-azoli**

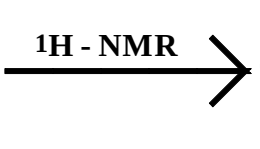
Echilibrul	Marimea de definitie	NH	S	O
	pKb → pKa ←	11.5 2.5	14.5 - 0.5	17.0 - 3.0
	pKa → pKb ←	14.2 - 0.2	- -	- -
	pKb → pKa ←	7.0 7.0	11.5 2.5	13.2 0.8
	pKa → pKb ←	14.4 - 0.4	- -	- -



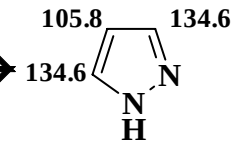
pyrazole
as *neutral* form



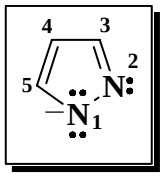
π – charges



δ – values (ppm)

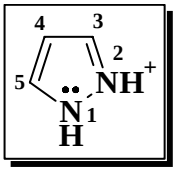


δ – values (ppm)

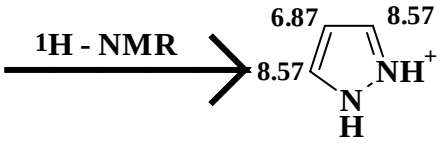


pyrazole
as *anionic* form

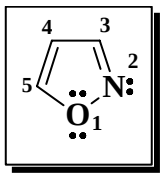
δ – values (ppm)



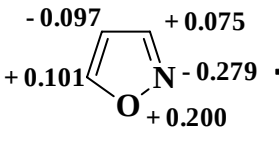
pyrazolium cation



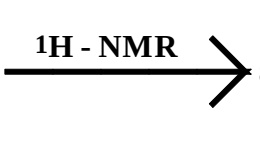
δ – values (ppm)



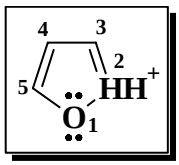
izoxazole
as *neutral* form



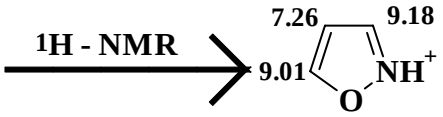
π – charges



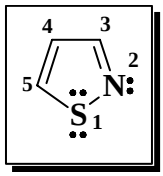
δ – values (ppm)



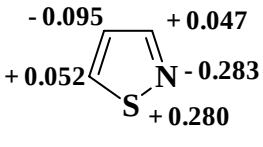
izoxazolium cation



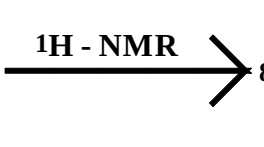
δ – values (ppm)



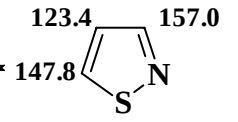
izothiazole
as *neutral* form



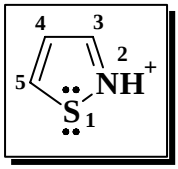
π – charges



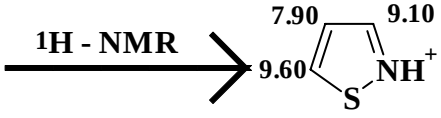
δ – values (ppm)



δ – values (ppm)



izothiazolium cation



δ – values (ppm)

Nota 1: influenta α **- vecinatatii heteroatomilor** se face resimtita mai mult asupra valorilor **pKa** ale speciilor protonate (**1,3 - azolii protonati** sunt specii **mai slab acide** decat **1,2 - azolii protonati**)

Consecinta 1: functionalizarea prin **SE la –*C*H=** heterociclic se realizeaza in **conditii mai putin dure**

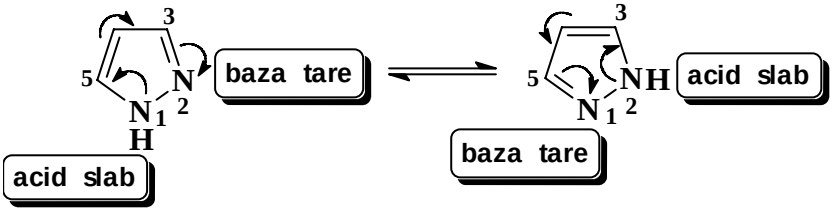
Nota 2: influenta α **- vecinatatii atomilor de azot** este nesemnificativa asupra valorilor **pKa** ale speciilor neutre (**pirazol** *vs*. **imidazol**).

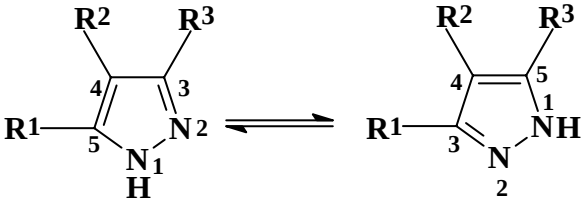
Nota 3: in ambele cazuri se manifesta direct **efectul –I** al heteroatomului **X** asupra **azotului piridinc** (**paralelism accentuat** intre **intensitatea efectului –I** si **valorile pKb** ale **speciilor neutre)**

c) tautomeria pirazolilor:

-fenomen dinamic rapid (tautomerie prototropica) in scala de timp spectrala

- **consecinta: echivalenta pozitiilor *C*-3** si ***C*-5** in cazul derivatilor **mono-, di-** sau **tri- *C*-substituiti**

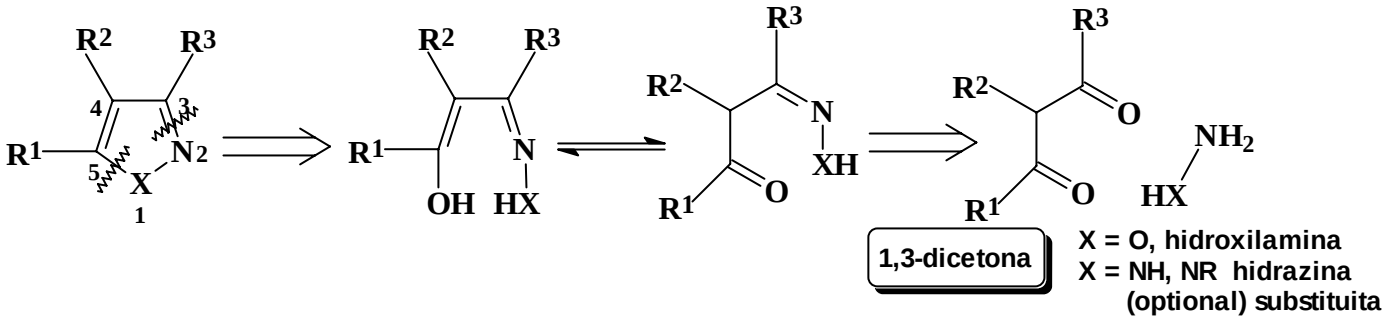




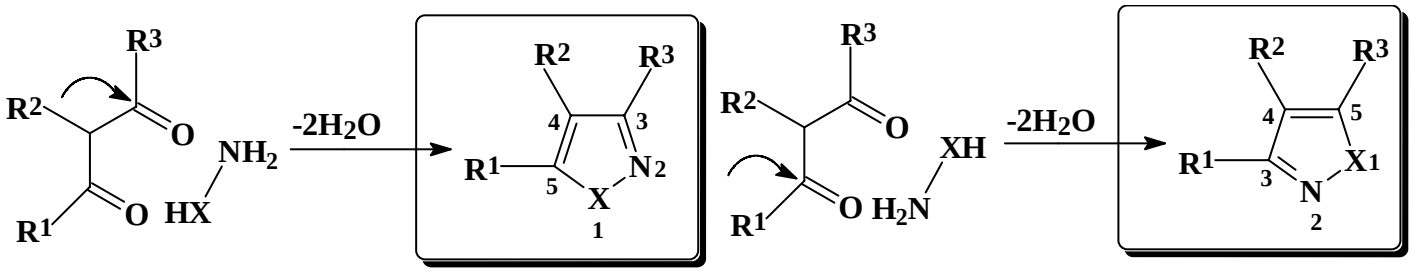
2. Sinteze:

2.1. Izoxazoli si pirazoli:

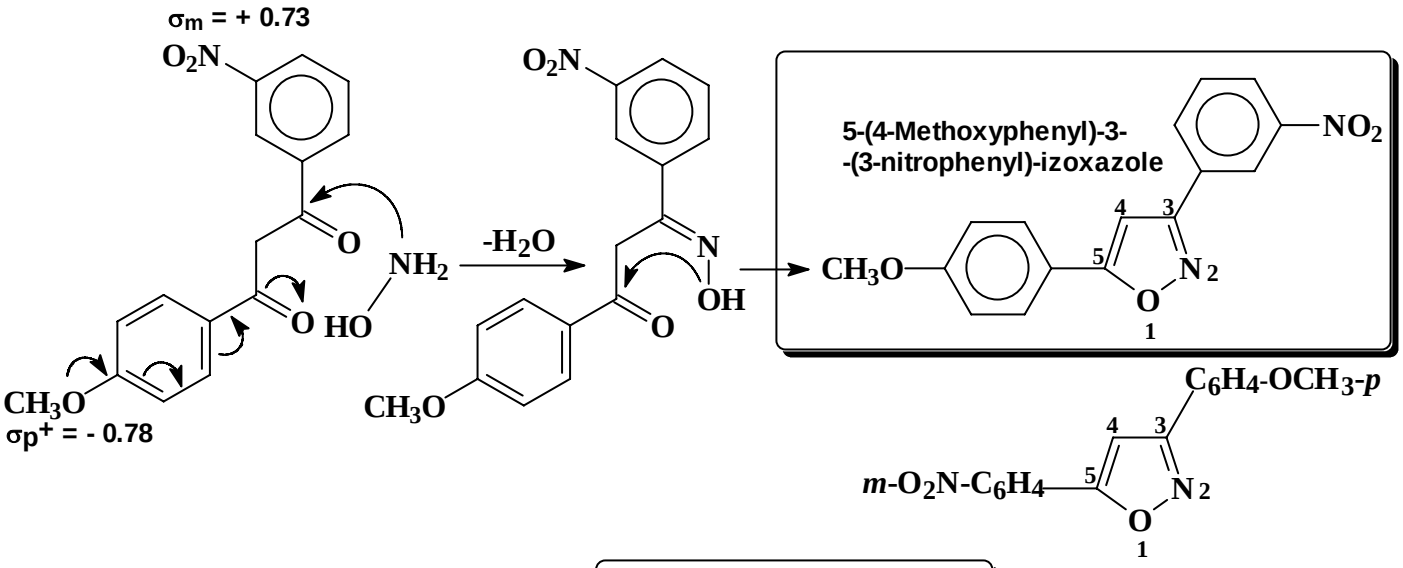
a) deconectare hidrolitica: (1-5)-(2-3)

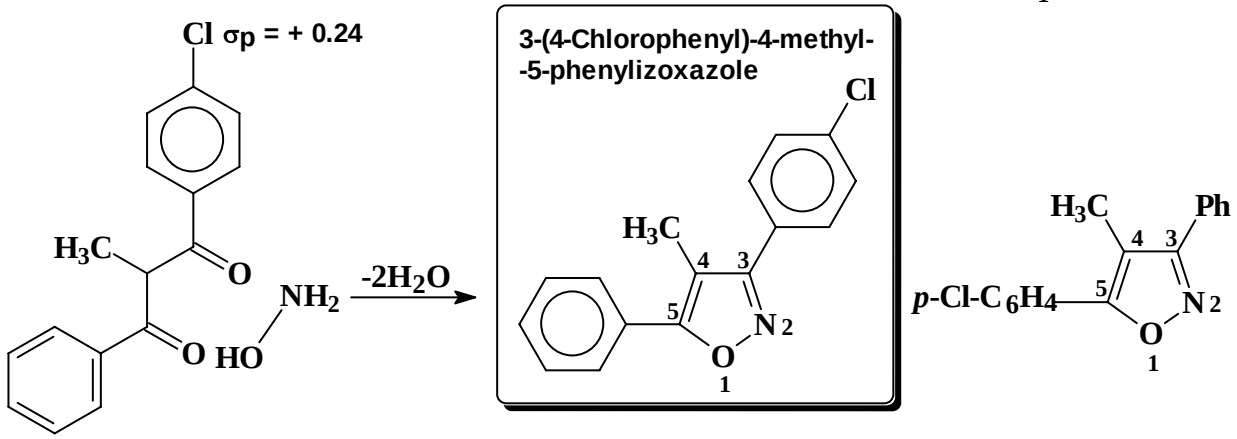


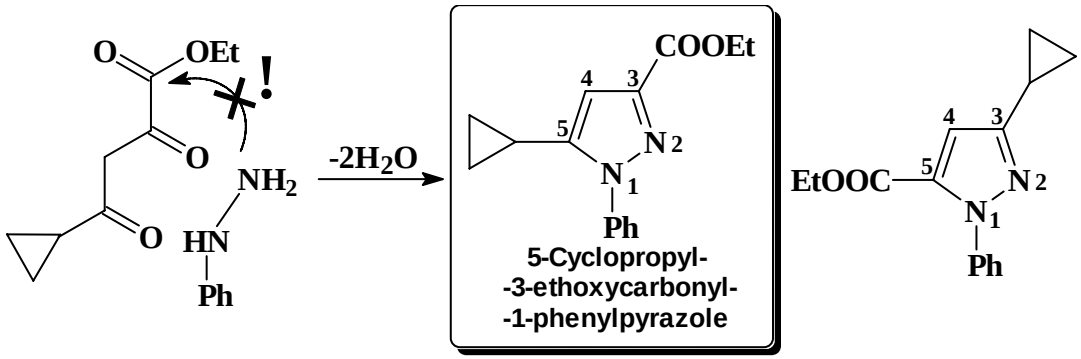
-aspect particular: *r e g i o s e l e c t i v i t a t e a* ciclizarii daca $R^1 \neq R^2 \neq R^3$ si $X \neq NH$



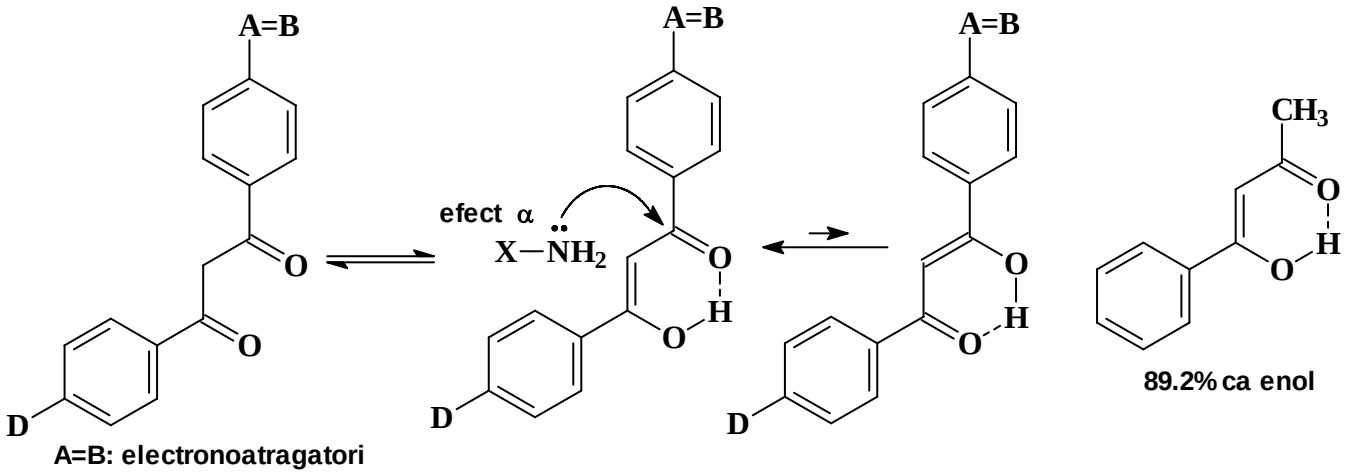
- se formeaza cu **larga majoritate regioizomerul** provenit din **atacul nucleofil** al aminei asupra **carbonilului cel mai electrofil**







Rolul tautomeriei substratului:



Procese *model* de cicloaditie [4 + 2] 1,3 - dipolara

1. *Aditia anionului alil la etena*

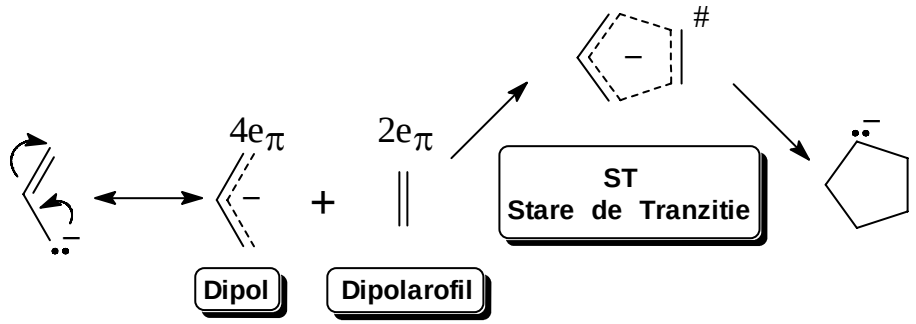
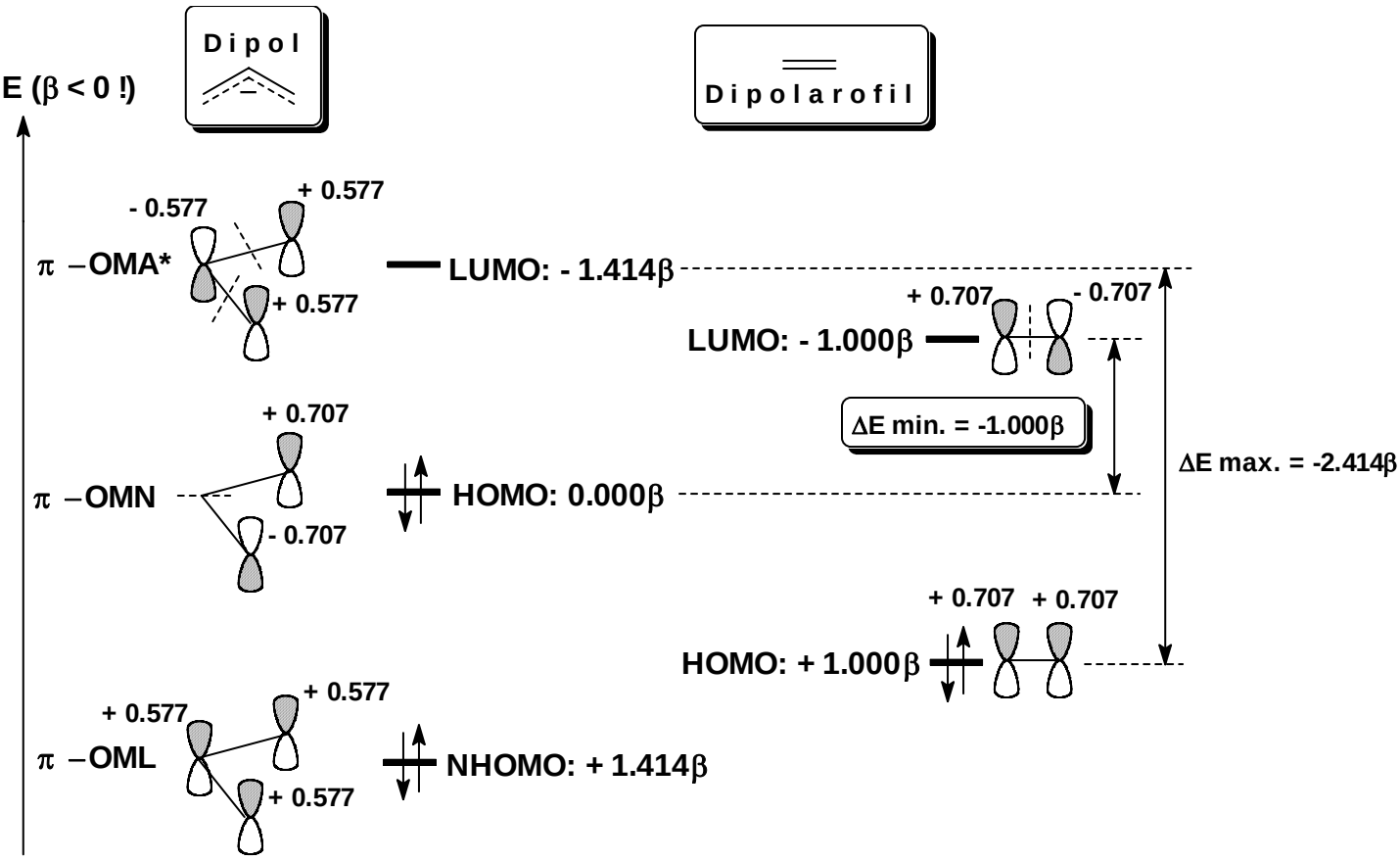
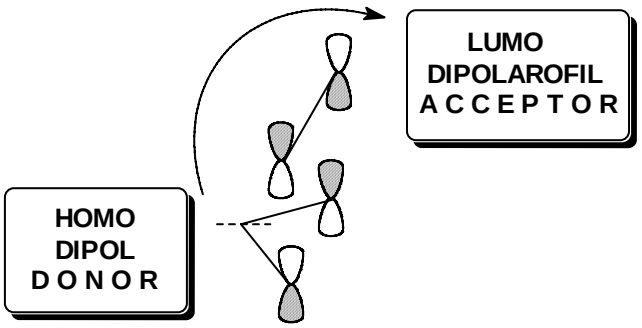


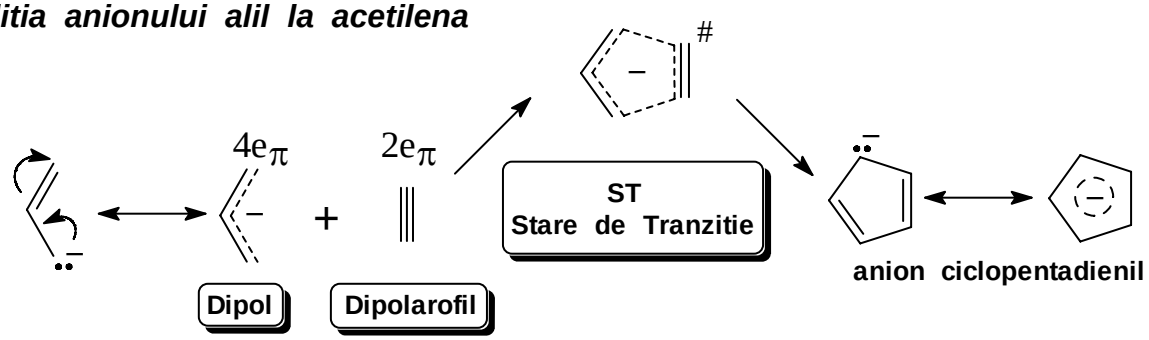
Diagrama energetica a ocuparii orbitalilor din partenerii de reactie:



ΔE min. (LUMO - HOMO) ⟶ orbitali s t e r e o d i r e c t o r i: - 1.000 β



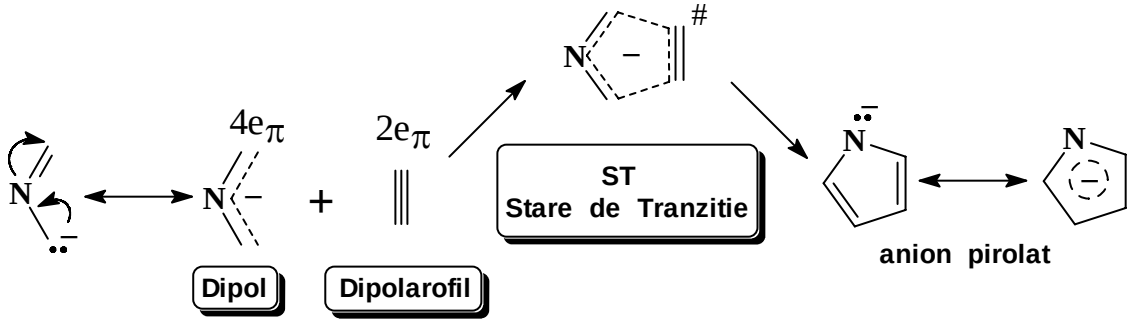
2. Aditia anionului alil la acetilena



OMF implicati	LUMO	HOMO
Anion alil	- 1.414β	**0.000β**
Acetilena	**- 1.300β**	+ 1.500β

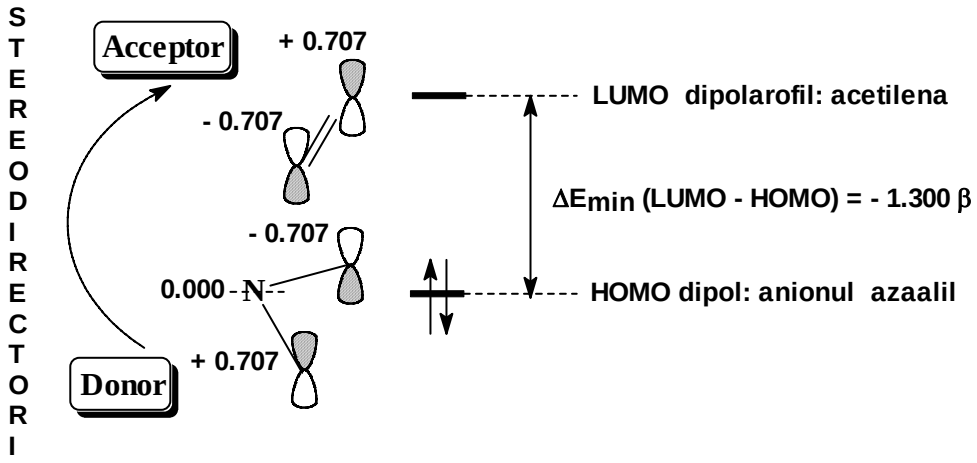
ΔE_{min} (LUMO - HOMO) = - 1.300 β

3. Aditia anionului <u>azaa</u>lil la acetilena



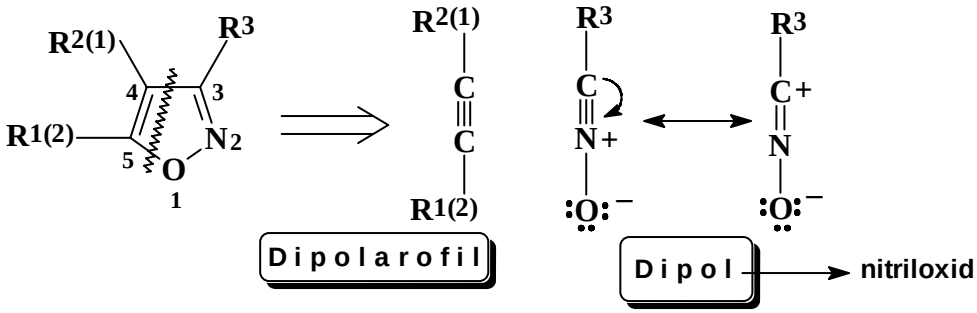
OMF implicati	LUMO	HOMO
Anion azaalil	- 1.117β	**0.000β**
Acetilena	**- 1.300β**	+ 1.500β

ΔE_{min} (LUMO - HOMO) = - 1.300 β

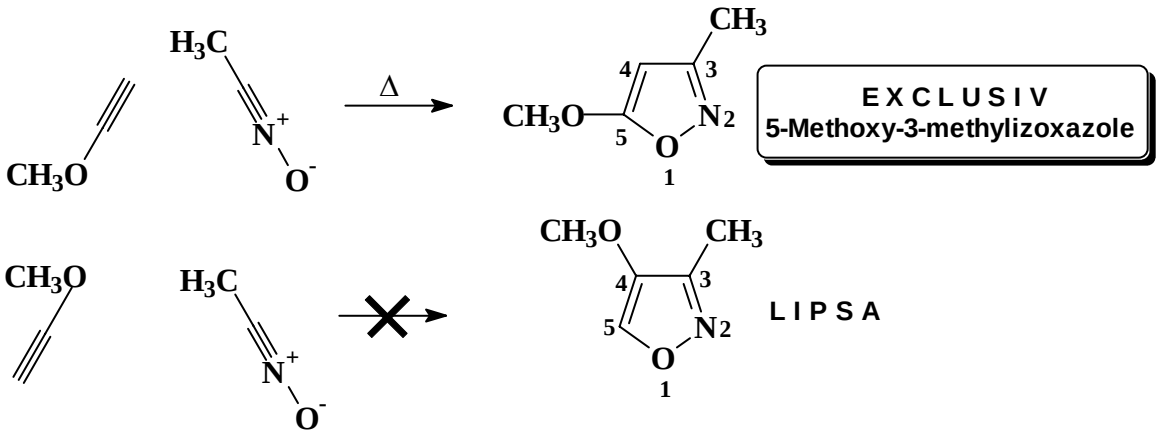


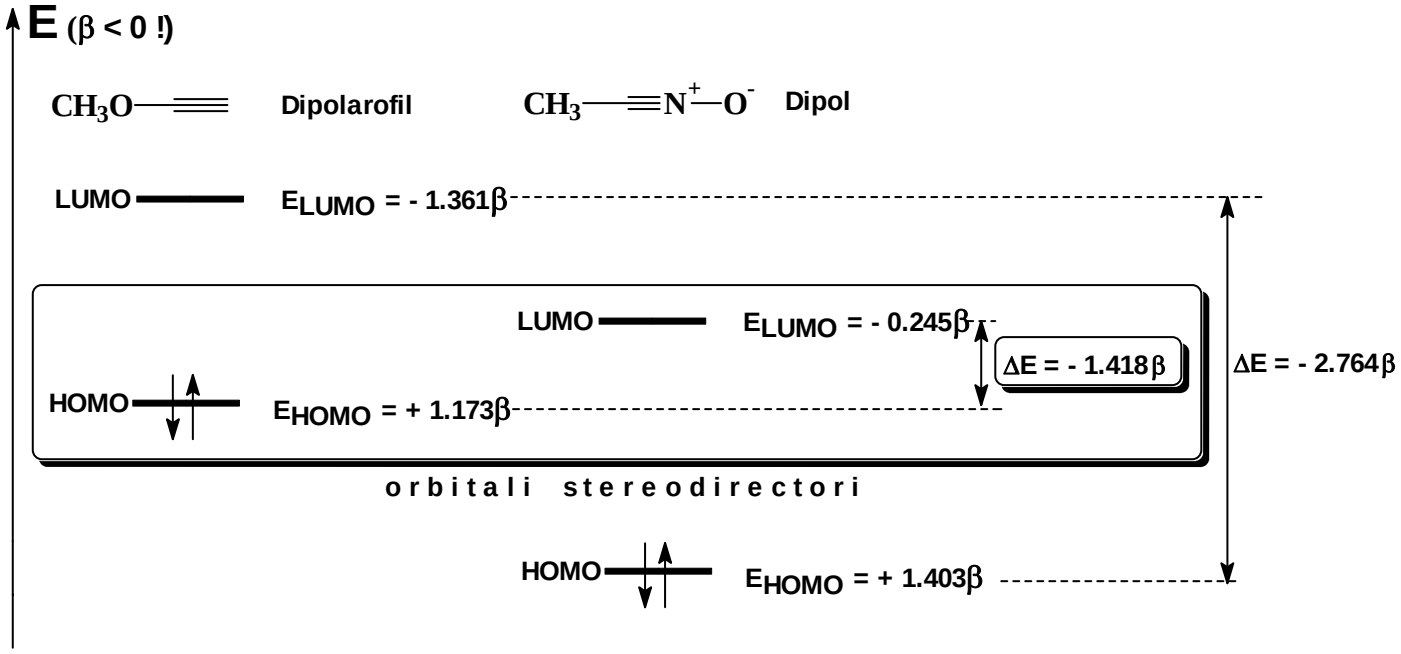
Limitele teoriei: in pofida faptului ca diferentele de energie minime **calculate** (LUMO – HOMO) **sunt aceleasi in ambele cazuri**, **numai aditia anionilor azaalil (substituiti)** se cunoaste la acetilena

-b) izoxazoli; deconectarea ca proces *retro* Diels - Alder: (1-5)-(3-4)

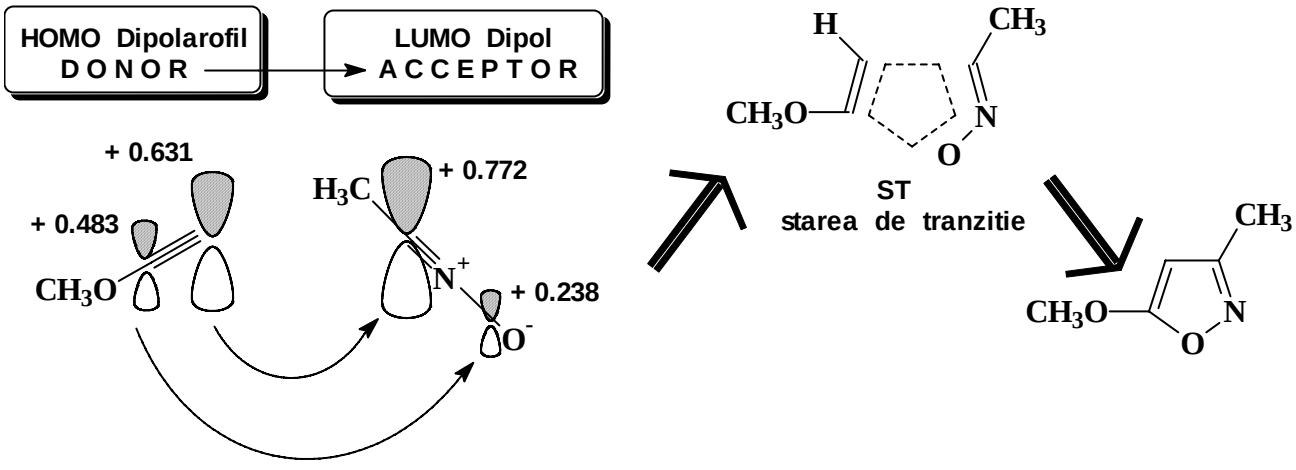


Exemplul 1:





min. ΔE [$E_{LUMO} - E_{HOMO}$ adica - 1.361β – (+1.403β) si - 0.245β – (+ 1.173β)] = **–1.418β**



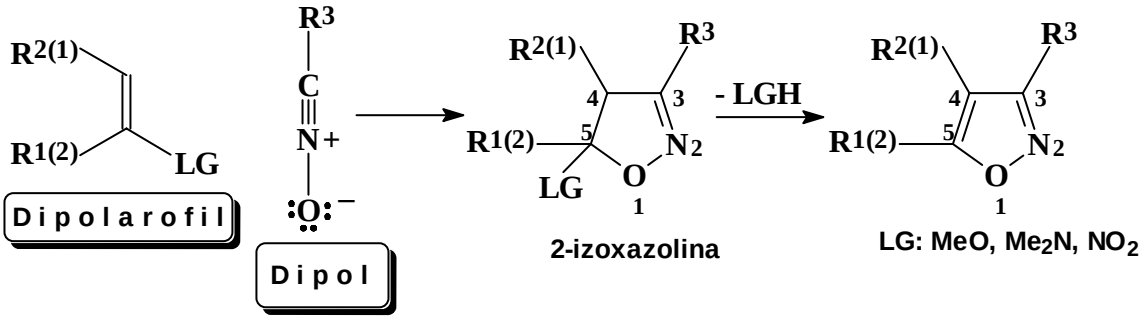
Nota 1: tipul reactiei → **cicloaditie 1,3-dipolara [4 + 2]**

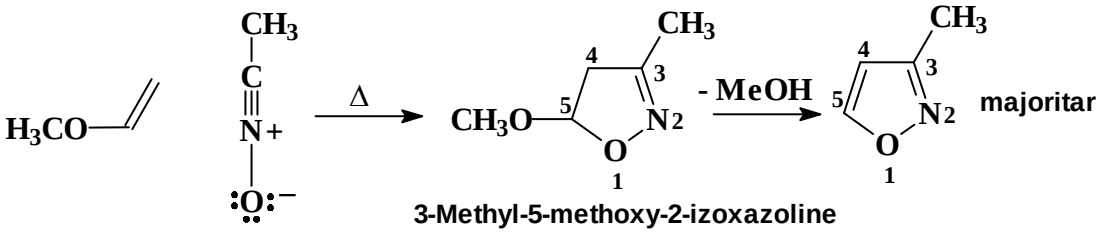
Nota 2: tipul interactiei → **donor** (HOMO Dipolarofil) – **acceptor** (LUMO Dipol) intre **orbitalii stereodirectori** care asigura **cu cea mai mare probabilitate** starea de tranzitie **ST**.

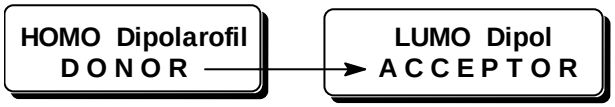
Nota 3: celalalt regioizomer, in acest caz, este **total** absent **datorita diferentei energetice discrepante** intre cele doua interactii perturbationale (HOMO – LUMO) posibile (-1.418β *vs*. -2.764β); el corespunde celeilalte perechi de orbitali (LUMO Dipolarofil – HOMO Dipol).

Exemplul 2:

- dipolarofilul ca **alchena functionalizata**

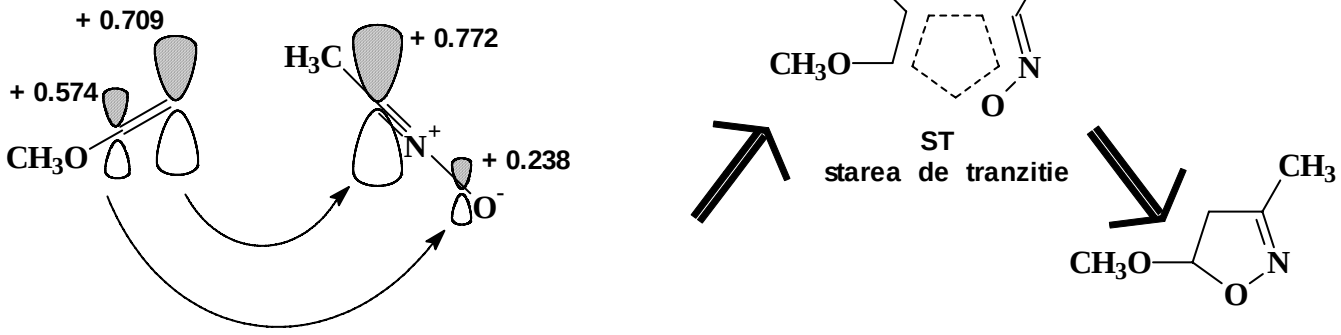




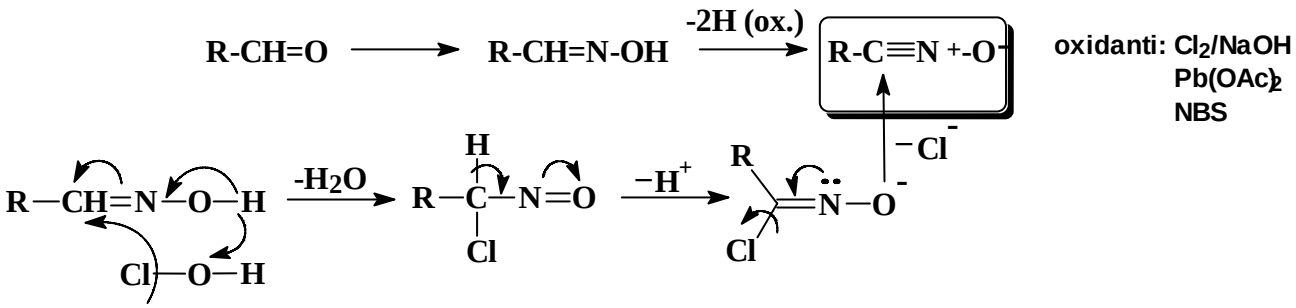


E_{HOMO} (+ 0.809β) **E_{LUMO} (- 0.245β)** **$\Delta E_{(LUMO - HOMO)}$ = - 1.054β orbitalii stereodirectori**

E_{LUMO} (- 1.068β) E_{HOMO} (+ 0.403β) $\Delta E_{(LUMO - HOMO)}$ = - 2.471β

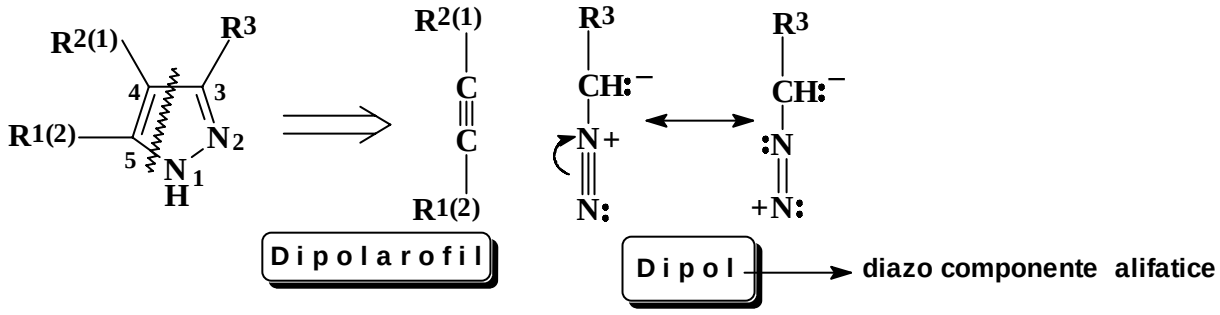


- generarea ***in situ*** a nitriloxizilor (R = aril, alchil)



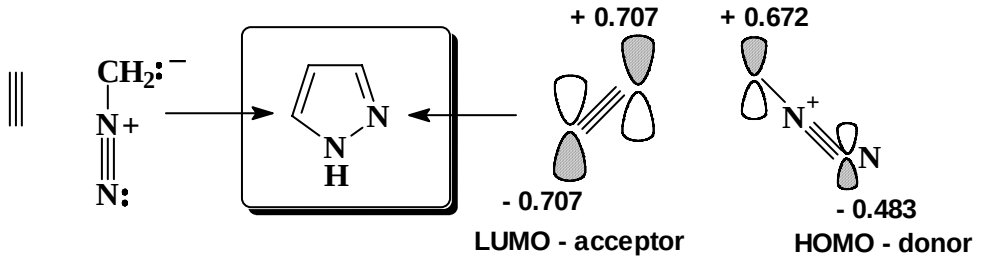
c) pirazoli; retrosinteza: deconectarea ca reactie ***retro* Diels - Alder: (1 - 5) - (3 - 4)**

- sinteza: cicloaditie 1,3-dipolara [4 + 2] intre **alchine (functionalizate)** si **diazo componente alifatice** (diazometan, ester diazoacetic, etc); acestea din urma se prepara, uzual, *in situ*



Exemplul 1:

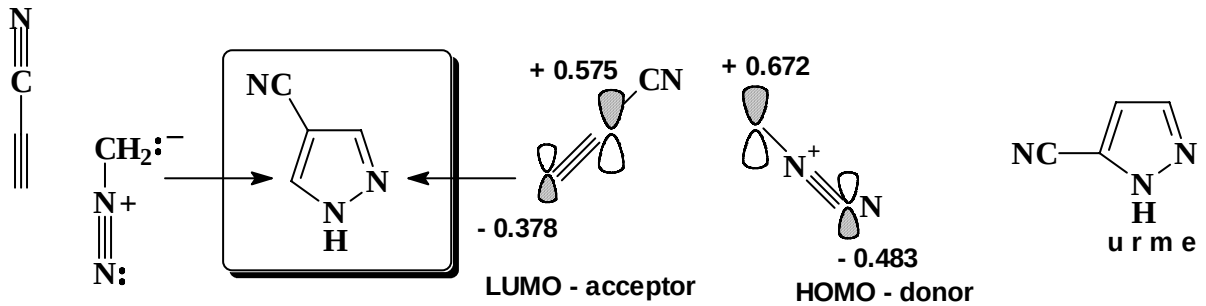
- sinteza pirazolului ca atare:



Orbitali stereodirectori (β)	E_{HOMO}	E_{LUMO}	
Acetilena	+ 1.500	**- 1.300**	→ **ΔE = -1.836β**
Diazometan	**+ 0.536**	- 0.924	

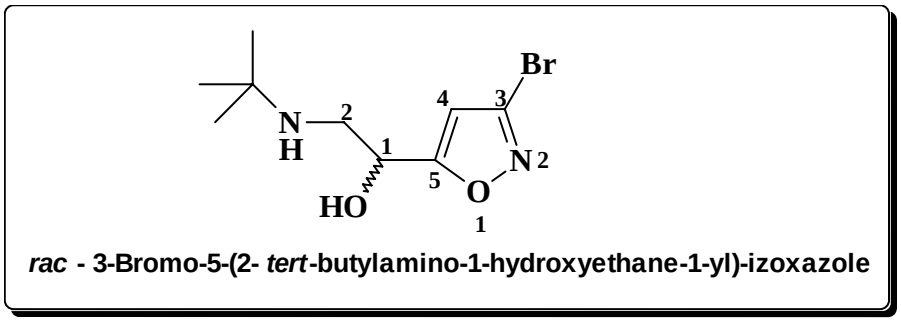
Exemplul 2:

- regioselectivitate **practic totala** la prepararea 4-cianopirazolului



Orbitali stereodirectori (β)	E_{HOMO}	E_{LUMO}	
Nitrilul acidului propiolic	+ 1.132	**- 0.920**	→ **ΔE = -1.456β**
Diazometan	**+ 0.536**	- 0.924	

IMPORTANTA CICLOADITIILOR 1,3 - DIPOLARE [4 + 2] IN SINTEZA 1,2 – AZOLILOR INALT FUNCTIONALIZATI

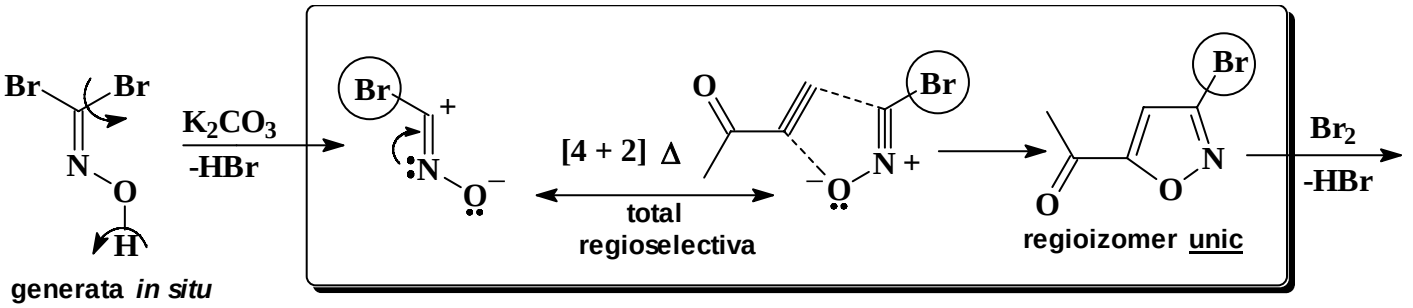


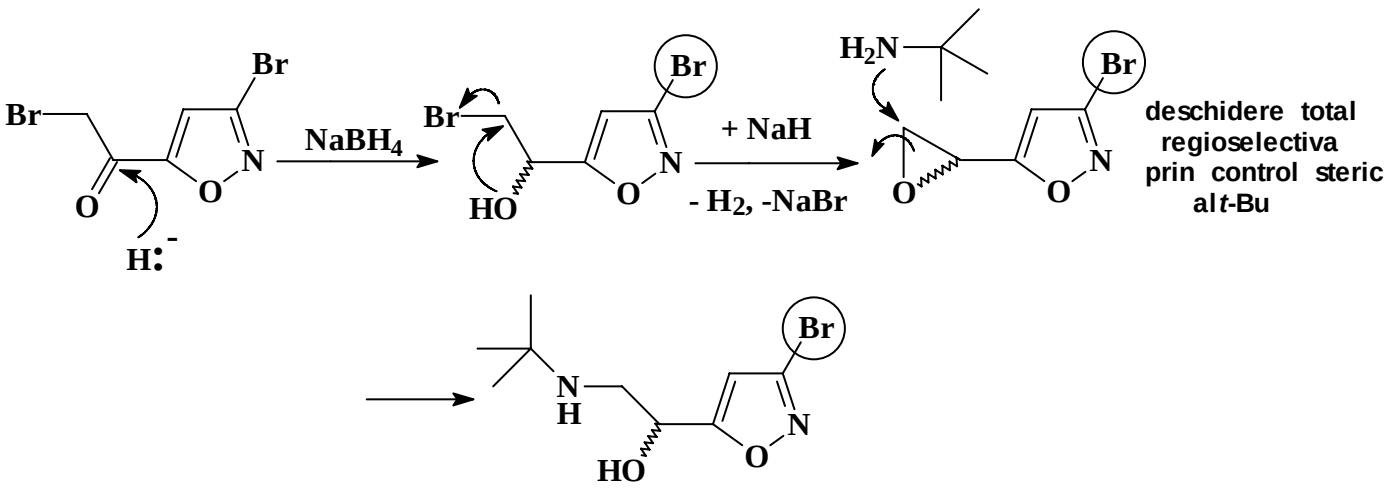
***rac* - 3-Bromo-5-(2- *tert*-butylamino-1-hydroxyethane-1-yl)-izoxazole**

Smith Kline Beecham Pharmaceuticals®

Preparat utilizat la tratarea astmului bronsic

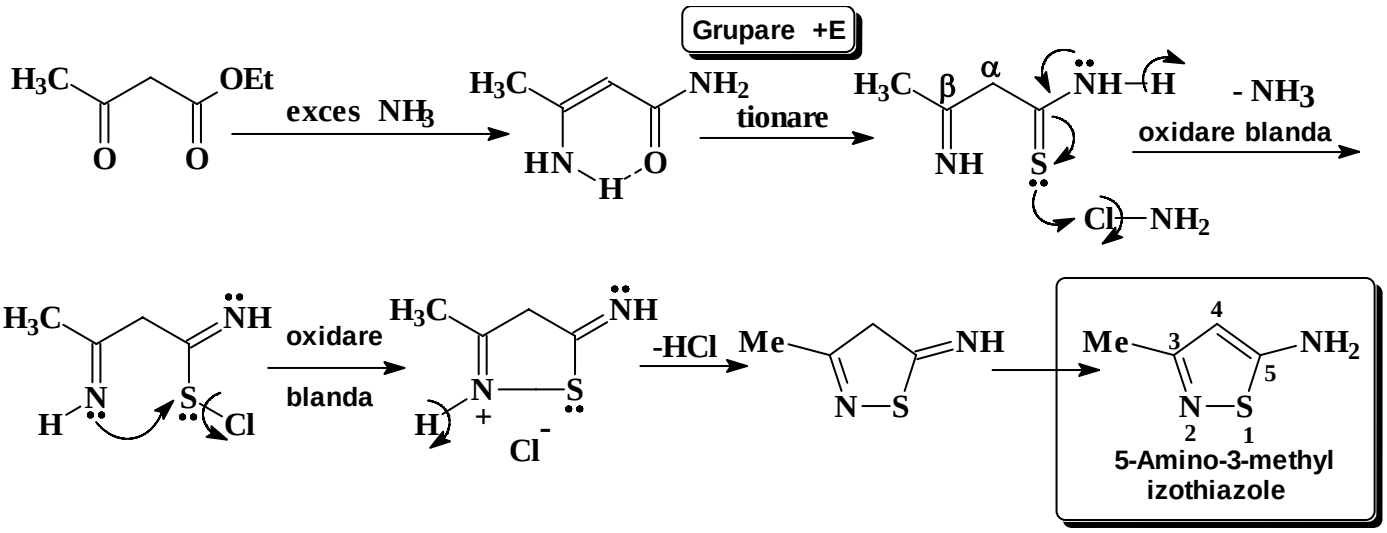
Problema: introducerea **atomului de brom la *C*-3 nu este posibila** pe **heterociclul preformat**; el trebuie sa se gaseasca pe un precursor convenabil.





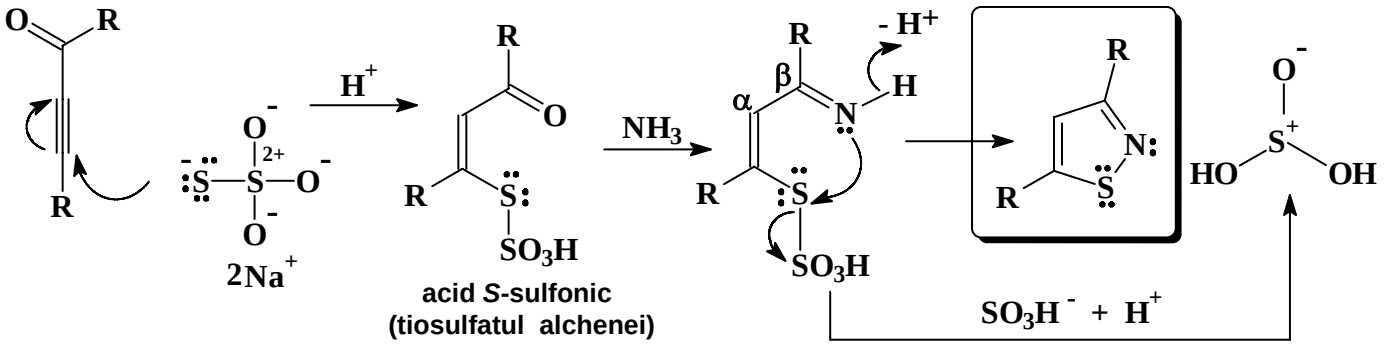
2.2. Izotiazoli:

a) ciclizarea redox a β - iminotioamidelor:



Nota: tiolamina ca **H_2N-SH** este prea **instabila → legatura N - S Nu este p r e f o r m a t a**

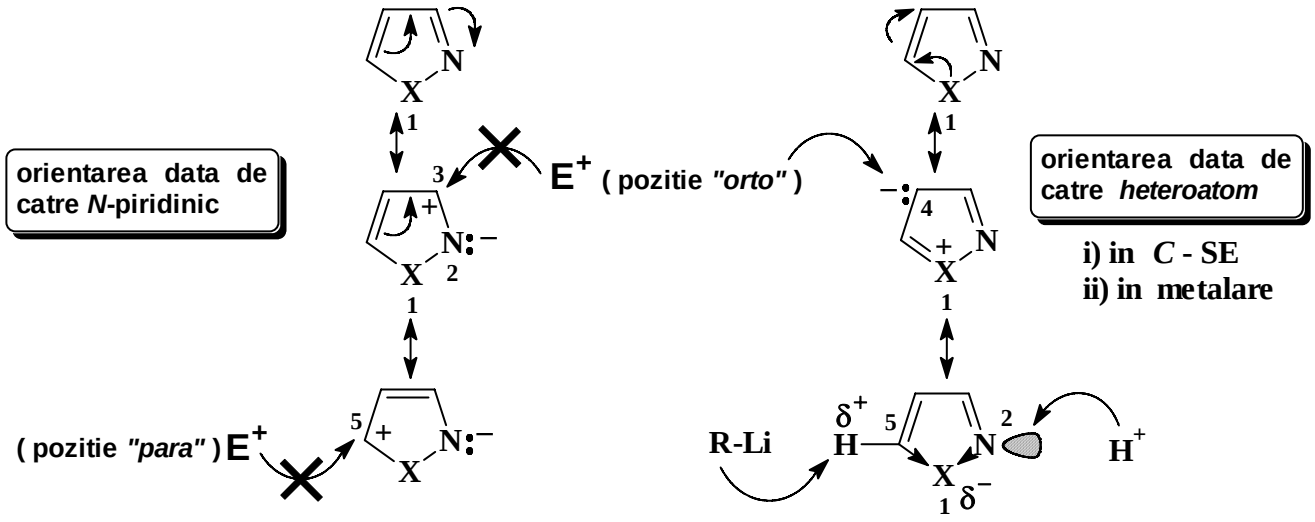
b) ciclizarea redox a acizilor β - imino - *S* - sulfonici:



Nota: R (identici sau diferiti, alchil, aril)

3. Functionalizarea:

- delimitarea si discriminarea centrelor reactive din 1,2-azoli:



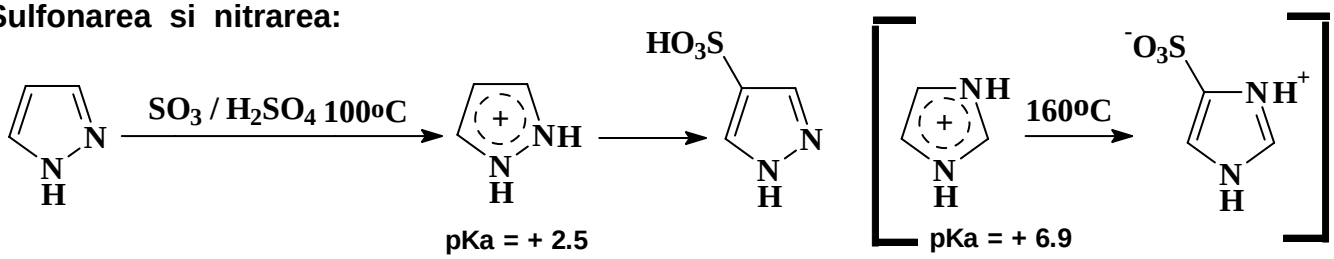
Nota 1: la functionalizarea prin **SE** la **–*C*H=** se manifesta **– E (*N* - piridinic) dominant** fata de **+ E_X** (ca **S > NH > O**) → orientare la ***C* - 4** ("*Meta* Directing Group stronger than the *Ortho* Directing Group")

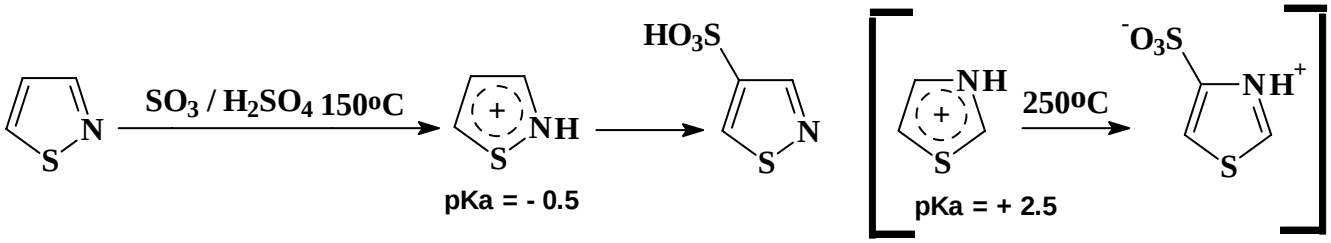
Nota 2: la functionalizarea *via* metalare se **manifesta – I_X** → orientare la ***C* - 5**

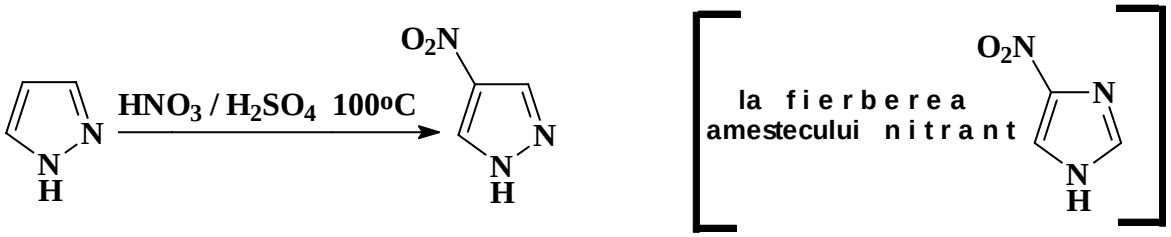
Nota 3: atacul electrofil la *N* - piridinic se manifesta **mai ales prin protonare** ca o consecinta a diminuarii **nucleofilicitatii** acestui centru prin **α - vecinatatea efectului –I_X** (ca O > S > NH)

3.1. Functionalizarea prin SE la *C*-4:

a) Sulfonarea si nitrarea:



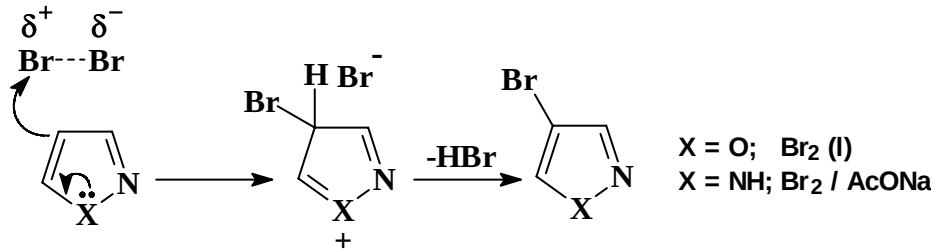




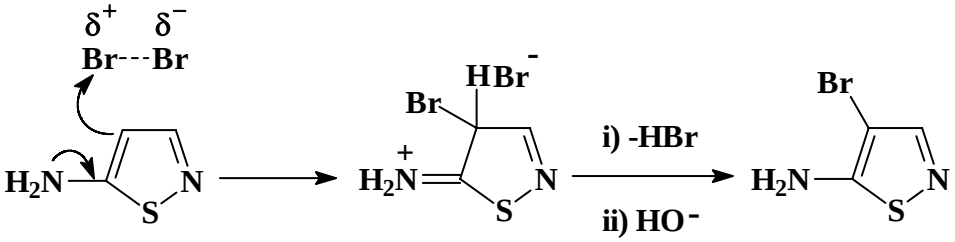
Nota: se mentin conditiile **dure**, similare 1,3-azolilor

b) Halogenarea:

- numai **bromurarea** prezinta interes preparativ (vezi interschimbul halogen – metal)

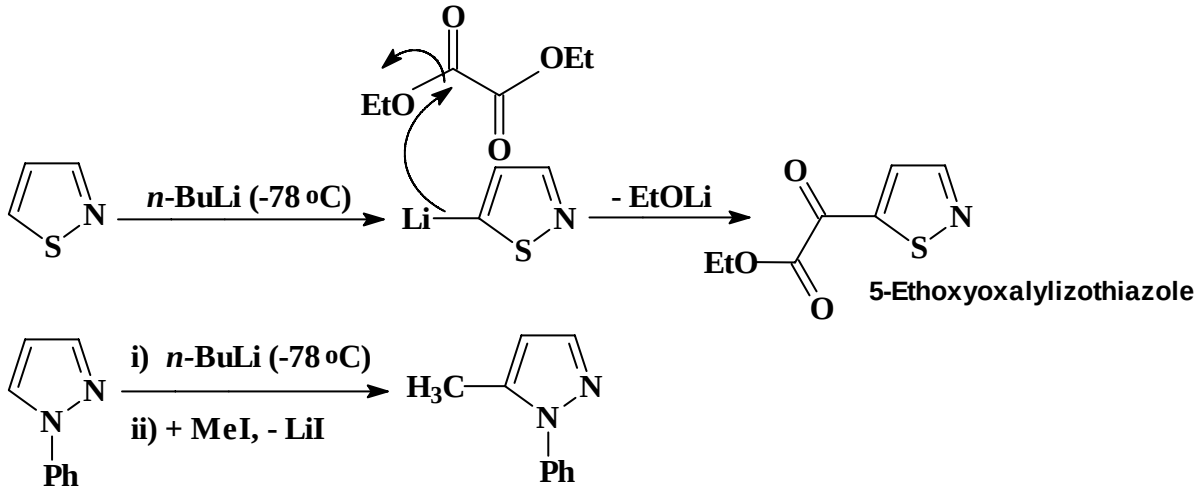


- facilitarea substitutiei de catre un **presubstituent activant:**

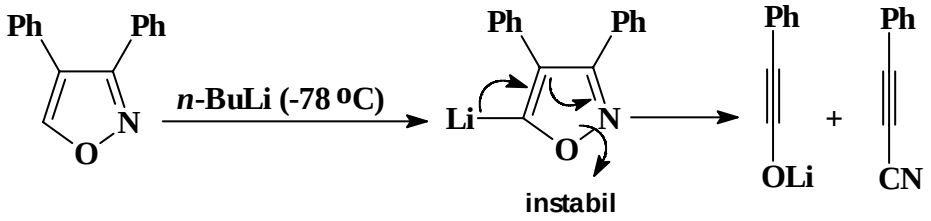


3.2. Functionalizarea prin metalare:

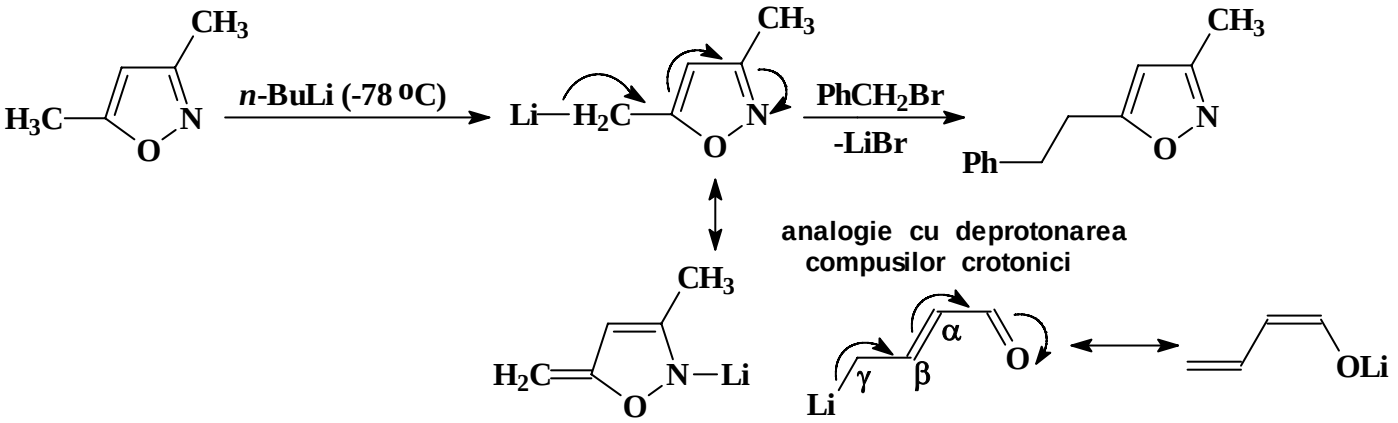
a) are loc la ***C* - 5** si este valabila numai pentru **pirazoli *N* - substituiti** si **izotiazoli deoarece…**



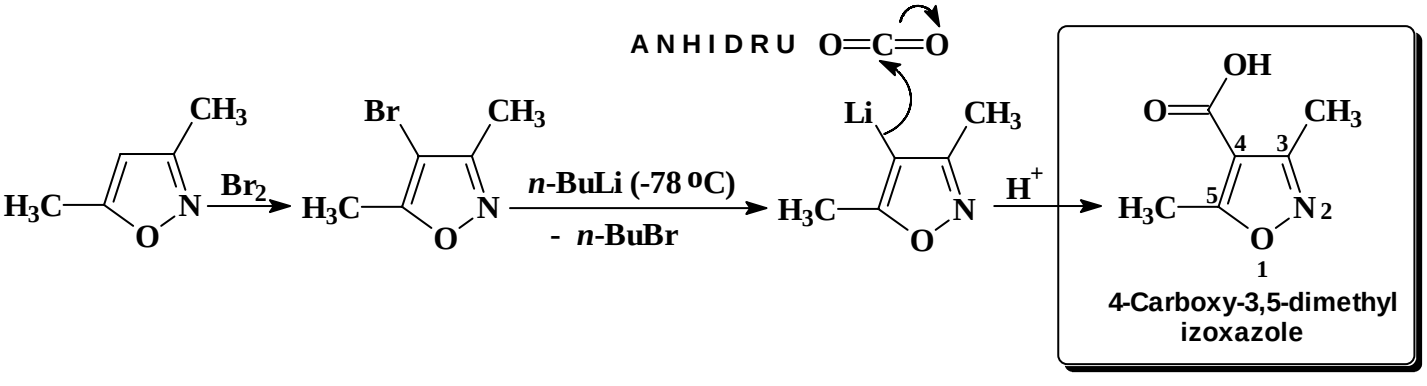
b) …in **cazul particular** al izoxazolilor, litioderivatul se descompune, **de exemplu:**



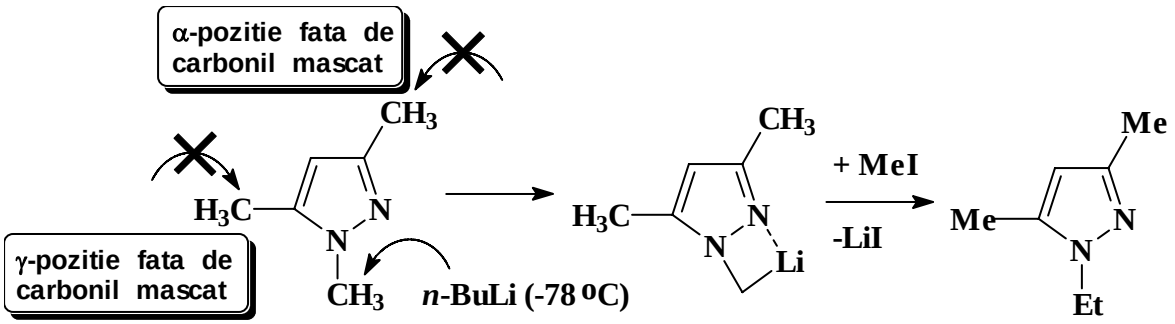
c) carbanioni stabilizati de catre heteroatomi apartinand pentaheterociclului 1,2 - azolic: - numai izoxazolii (NU si **pirazolii** sau **izotiazolii) stabilizeaza carbanionii** rezultati prin deprotonarea unei **grupe metil** de la ***C* - 5 (γ - stabilizare)**



- crearea indirecta de **carbanioni la C - 4** prin **interschimb halogen (polarizabil)** – **metal**



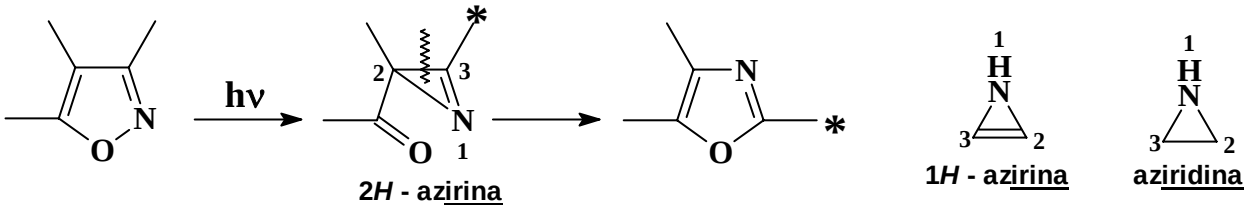
- unii **pirazoli *N* - <u>metilati</u> pot stabiliza carbanioni** prin **deprotonarea selectiva** a **acestei grupe (α - stabilizare)** in prezenta altora**:**



4. Reactii de rearanjare de schelet:

- **Nu au** valoare preparativa
- sunt reactii **electrociclice permise fotochimic**
- sunt cunsocute **doua mecanisme** principale prin care **unii 1,2-azoli** se transforma in **1,3-azoli:**

a) izoxazoli → oxazoli (*via* 2*H* - azirine):



b) izotiazoli → tiazoli (mecanism Walk):