PENTAHETARENES WITH 3, 4 HETEROATOMS

1. General

a) Typical representatives
b) Acid-base character of azoles with 3, 4 heteroatoms
c) Tautomerism of triazoles and tetrazole
d) Ring-chain tautomerism of azoles with 3, 4 heteroatoms

2. Main syntheses

2.1. Syntheses from precursors revealed by hydrolytic disconnections

2.1.1. 1,2,4-Oxadiazoles
2.1.2. 1*H*-1,2,4-Triazoles
2.1.3. 1,3,4-Triheteroazoles
2.1.4. 1,2,5-Triheteroazoles

2.2. Syntheses from precursors revealed by *Retro Diels & Alder* and related disconnections

2.2.1. Triheteroazoles: 1,2,3-thiadiazoles and 1*H*-1,2,3-triazoles
2.2.2. Tetraheteroazoles: 1,2,3,4-thiatriazoles and 1,2,3,4-tetrazoles (1*H* and 2*H*)
2.2.3. 1*H*-1,2,3-triazoles and 1*H*-1,2,3,4-tetrazoles by [4+2] 1,3-dipolar cycloadditions

2.3. Particular syntheses of tetraheteroazoles

2.3.1. *C*-5-Substituted 1*H*-1,2,3,4-tetrazoles by diazoniation
2.3.2. *C*-5-Substituted-1,2,3,4-thiatriazoles by *S*-nitrosation

3. Higher functionalisation

3.1. Functionalisation by electrophilic substitution

3.1.1. Functionalisation by electrophilic substitution at the ring carbon
3.1.2. Functionalisation by electrophilic attack at the ring nitrogen

3.2. Functionalisation by nucleophilic substitution

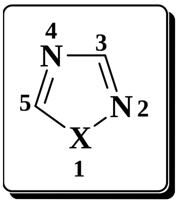
3.3. Functionalisation *via* metallation

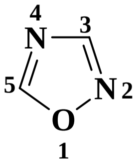
HETARENE PENTAATOMICE CU 3, 4 HETEROATOMI

1. Generalitati:

a) reprezentanti tipici:

seria 1,2,4:





1,2,4-oxadiazol

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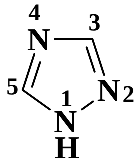

1*H*-1,2,4-triazol

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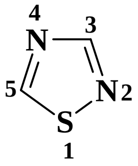
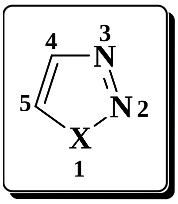
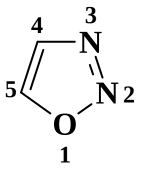


1,2,4-tiadiazol

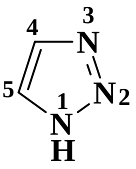
caracterul aromatic in crestere, paralel cu scaderea electronegativitatii heterotaomului 1

seria 1,2,3:

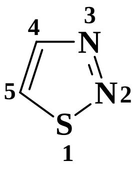




1,2,3-oxadiazol

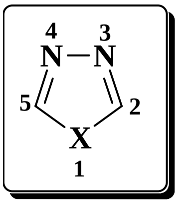


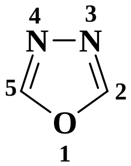
1*H*-1,2,3-triazol



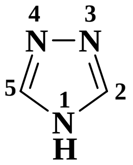
1,2,3-tiadiazol

seria 1,3,4:

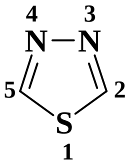




1,3,4-oxadiazol

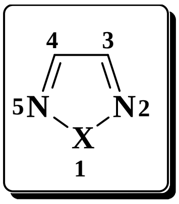


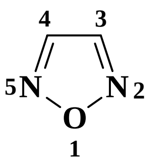
1*H*-1,3,4-triazol



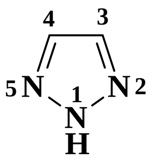
1,3,4-tiadiazol

seria 1,2,5:

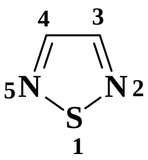




1,2,5-oxadiazol

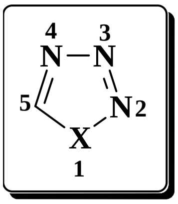


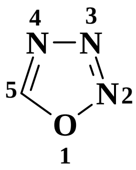
1*H*-1,2,5-triazol



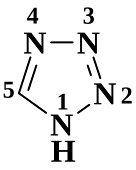
1,2,5-tiadiazol

seria 1,2,3,4:

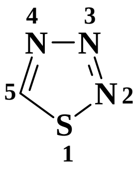




1,2,3,4-oxatriazol



1*H*-1,2,3,4-tetrazol



1,2,3,4-tiatriazol

Nota: **heteroatomul** care poarta **hidrogenul indicat (*H*)** are numarul de pozitie **cel mai mic; ceilalti heteroatomi de acelasi fel** primesc **cele mai mici numere posibile.**

Nota 1: au caracter aromatic; sunt compusi **diatropici** (**dar** valorile δ_H → **8 – 9ppm**)

Nota 2: contin cel putin **doi *N* – piridinici:**

Consecinta 1: **<u>diminuarea severa a caracterului bazic</u>** comparativ cu diazolii
Consecinta 2: **cresterea** semnificativa a caracterului acid in seriile **X = NH**
Consecinta 3: reactiile de functionalizare **SE** la **–C*H*=** → izolate si neimportante
Consecinta 4: reactiile de functionalizare **SE** la ***N* -piridinic**→ **importante**
Consecinta 5: functionalizarea prin **SE** ***via*** metalare → **fundamentala**

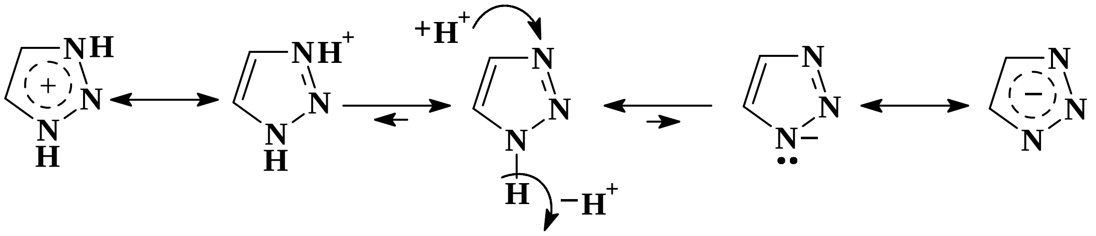
Nota 3: nu prezinta aceeasi importanta preparativa

Nota 4: nu prezinta aceeasi **stabilitate termodinamica**; aceasta **scade** odata cu:

a) cresterea numarului de heterotomi
b) scaderea caracterului aromatic in cazul **oxadi- si triazolilor**

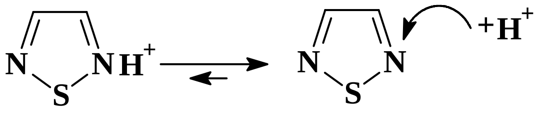
b) caracterul acido – bazic al azolilor cu 3, 4 heteroatomi:

Obs. : protonare preferentiala la *N*–piridinic **cel mai putin afectat** de vecinatatea altor azaatomi adiacenti (*e.g.* **–I$_{NH}$**).



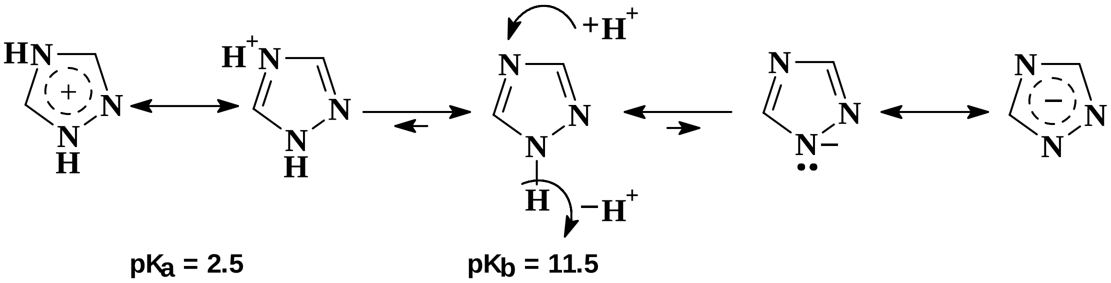
$pK_a = 1.2$ $pK_b = 12.8$
$pK_a = 9.3$ $pK_b = 4.7$

Obs. : reducerea **dramatica** a bazicitatii prin substituire ***N*H** cu ***S*** in seria **1,2,3**



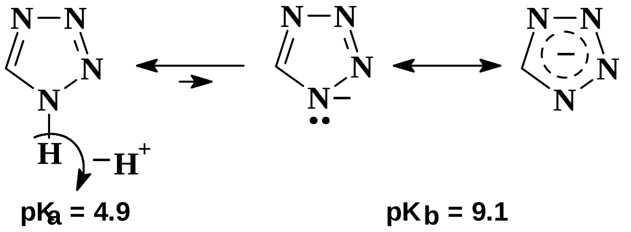
$pK_a = - 4.9$ $pK_b = 18.9$

Obs.: secventa de azaatomi 1,2,4 (≡ 1,3,4) prezinta o bazicitate mai mare decat succesiunea 1,2,3 (≡ 1,2,5, a se compara cu succesiunea 1,2 *vs*. 1,3 de la diazoli).



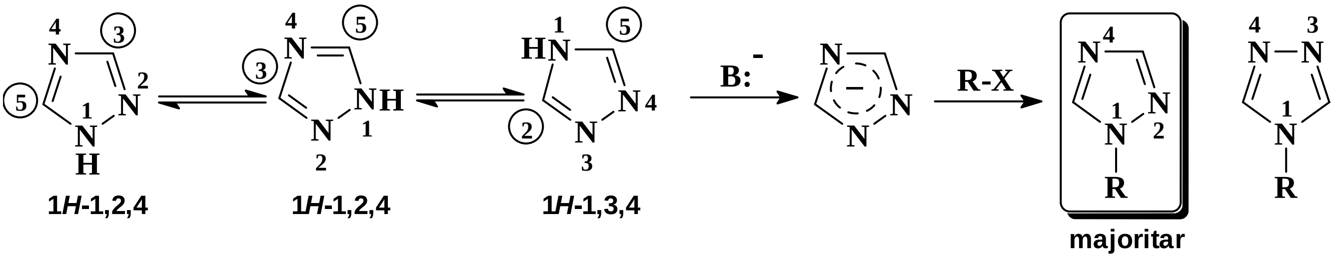
$pK_a = 2.5$ $pK_b = 11.5$
$pK_a = 10.0$ $pK_b = 4.0$

Obs.: Aciditatea tetrazolului este comparabila cu cea a acidului acetic !! (pKa ≈ 5)

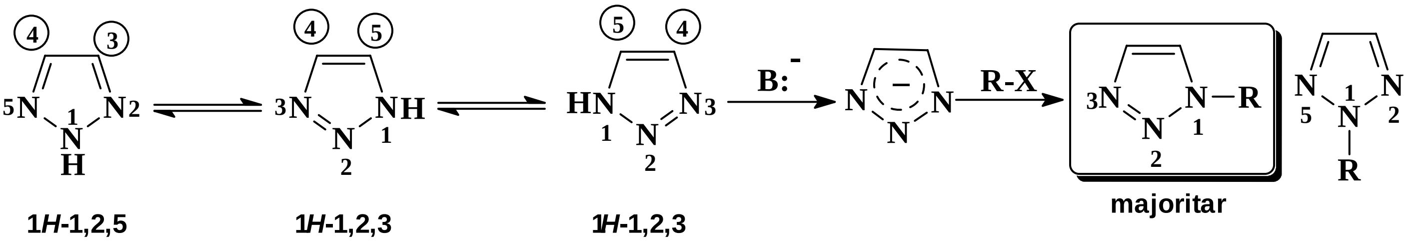


c) tautomeria triazolilor si tetrazolului:

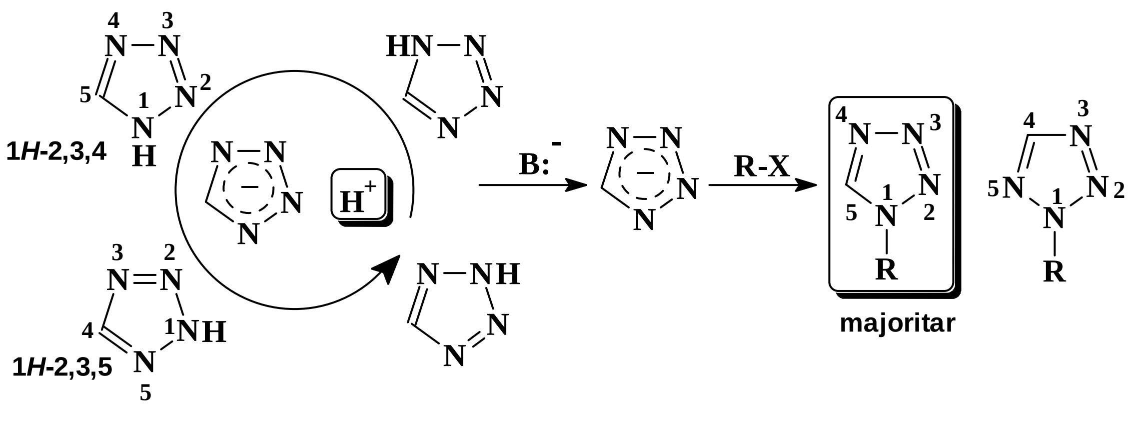
- tautomerie prototropica; acelasi fenomen rapid care face nediferentiabili tautomerii individuali in scala de timp spectrala



REGIOIZOMERII N*H* 1,2,4 *vs.* 1,3,4 sunt <u>nediferentiabili</u>
REGIOIZOMERII N*H* *C*-3 *vs.* *C*-5 *vs* *C*-2 substituiti sunt <u>nediferentiabili</u>
Sunt <u>diferentiabili</u> REGIOIZOMERII *N*-substituiti 1*H*-1,2,4 *vs.* 1*H*-1,3,4



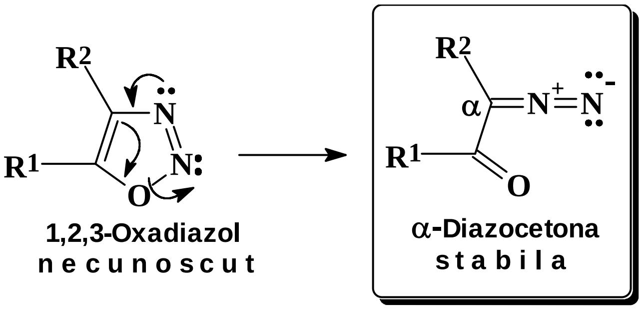
REGIOIZOMERII N*H* 1,2,5 *vs.* 1,2,3 sunt <u>nediferentiabili</u>
REGIOIZOMERII N*H* *C*-3 *vs.* *C*-4 *vs.* *C*-5 substituiti sunt <u>nediferentiabili</u>
Sunt <u>diferentiabili</u> REGIOIZOMERII *N*-substituiti 1*H*-1,2,3 *vs.* 1*H*-1,2,5



REGIOIZOMERII N*H* 1,2,3,4 *vs.* 1,2,3,5 sunt <u>nediferentiabili</u>
REGIOIZOMERII N*H* *C*-4 *vs.* *C*-5 substituiti sunt <u>nediferentiabili</u>
Sunt <u>diferentiabili</u> REGIOIZOMERII *N*-substituiti 1*H*-1,2,3,4 *vs.* 1*H*-1,2,3,5

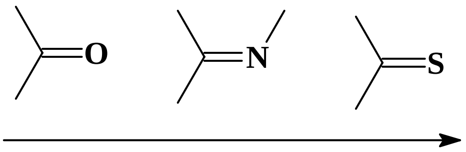
d) tautomeria inel – catena (*ring – chain tautomerism*) a azolilor cu 3, 4 heteroatomi:

- azoli cu 3 heteroatomi in secventa 1,2,3:

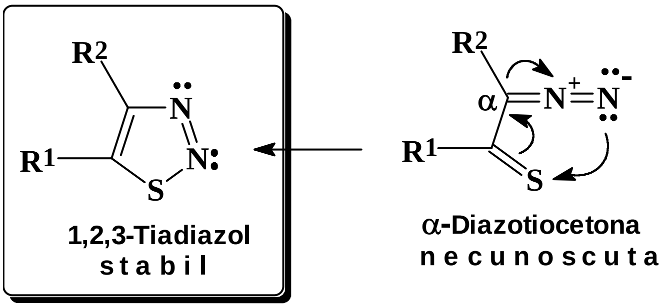


1,2,3-Oxadiazol
necunoscut

α-Diazocetona
stabila

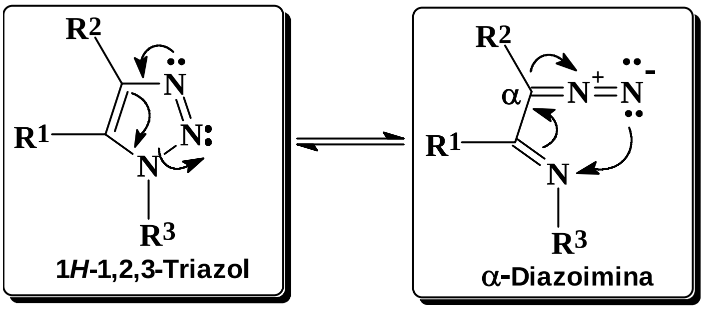


i) scade stabilitatea α-diazoderivatului
ii) creste stabilitatea heterociclului
iii) creste caracterul aromatic al heterociclului



1,2,3-Tiadiazol
stabil

α-Diazotiocetona
necunoscuta

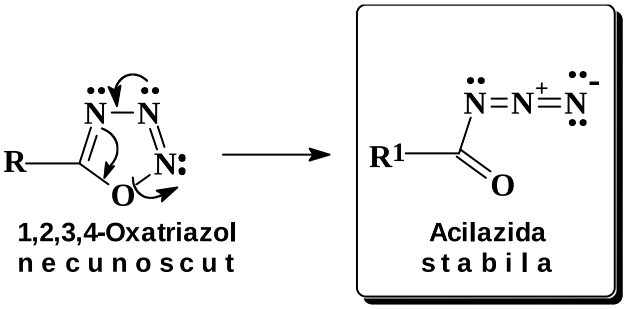


1*H*-1,2,3-Triazol

α-Diazoimina

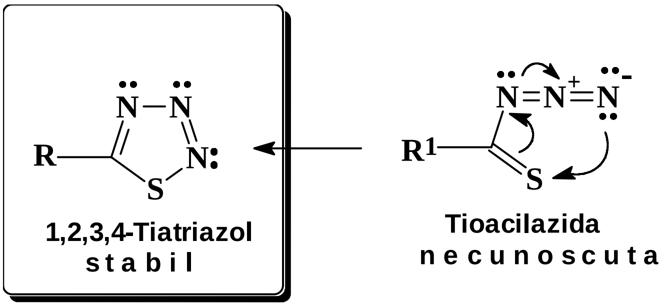
R^3 = H: stabil heterociclul
R^3 = puternic <u>electronoatragator</u>: echilibru

- **azoli cu 4 heteroatomi:** relatiile de stabilitate intre “tautomeri” sunt de acelasi tip si conditionate de aceiasi factori ca in cazul azolilor cu 3 heteroatomi.



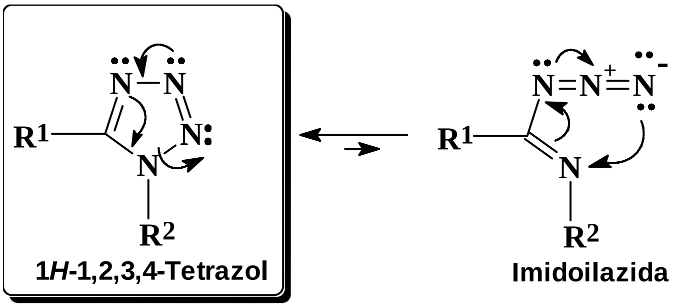
1,2,3,4-Oxatriazol
necunoscut

Acilazida
stabila



1,2,3,4-Tiatriazol
stabil

Tioacilazida
necunoscuta



1*H*-1,2,3,4-Tetrazol

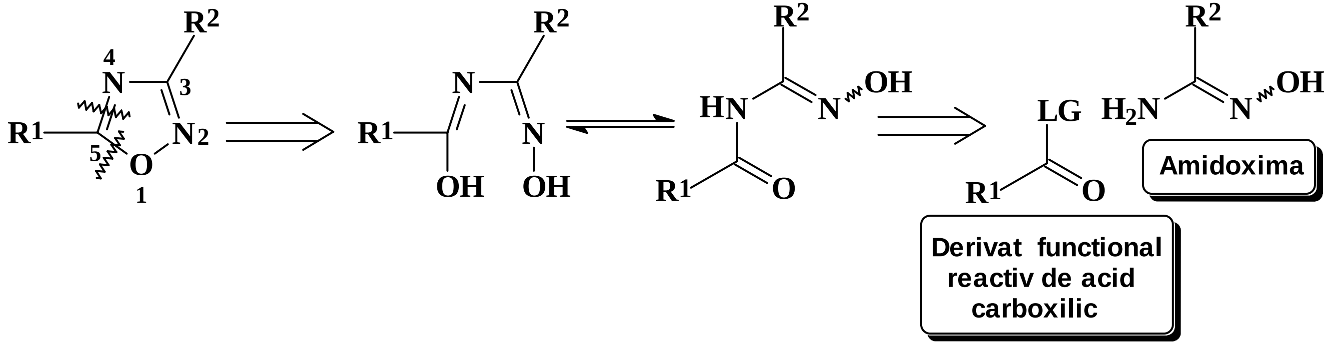
Imidoilazida

2. Principalele sinteze

2.1. Sinteze din precursori care admit deconectari hidrolitice

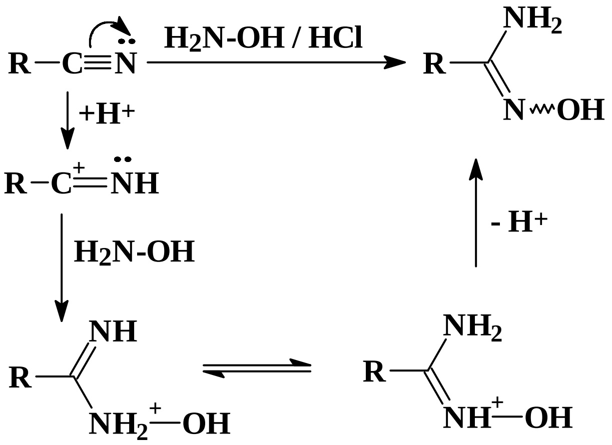
2.1.1. 1,2,4 – Oxadiazoli

- deconectare hidrolitica: (1 – 5) – (4 – 5)

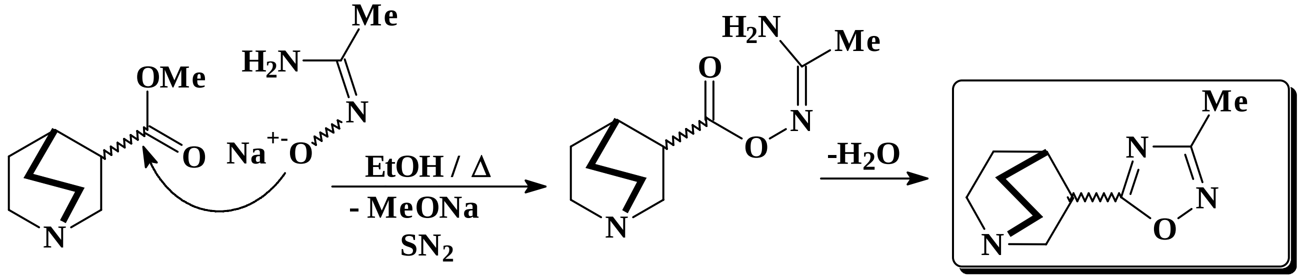


e.g. **LG = halo, OH, OR**

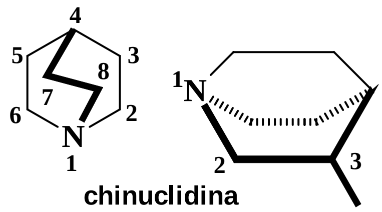
- **prepararea amidoximelor din nitrili:**



- **exemplu de aplicare “deturnata”(→ oxima sodata devine primul nucleofil)** (dupa SmithKline Beecham Pharmaceuticals®)



Preparat farmaceutic pentru tratarea dementei senile

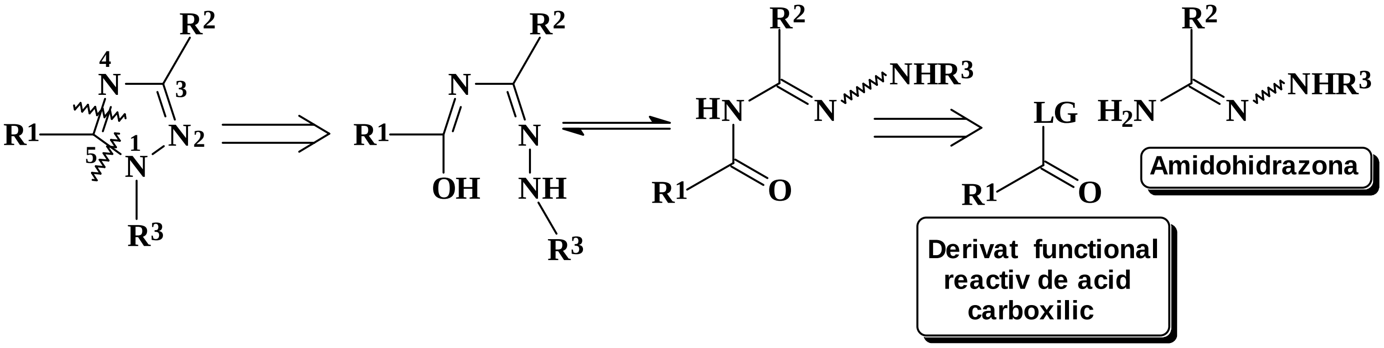


chinuclidina

1-Azabicyclo[2.2.0]octane-3-yl

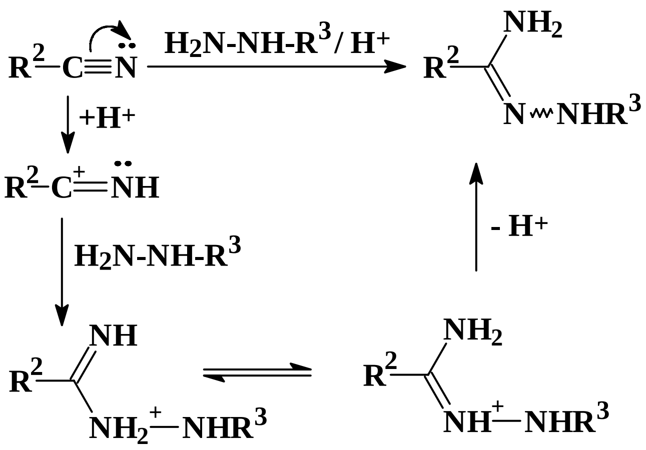
2.1.2. 1*H*-1,2,4 – Triazoli

- **deconectare hidrolitica: (1 – 5) – (4 – 5) identica** cu cea de la **1,2,4-oxadiazoli**



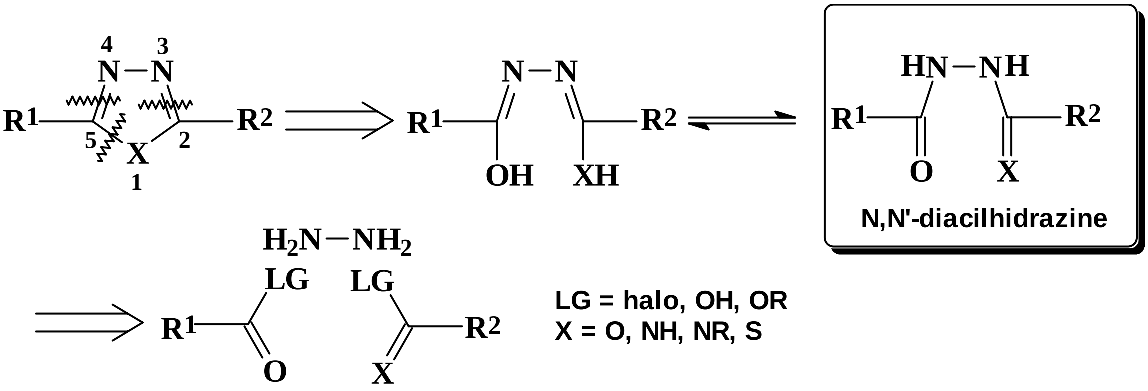
e.g. **LG = halo, OH, OR**

- **prepararea amidohidrazonelor din nitrili:**



2.1.3. 1,3,4-Triheteroazoli

- **deconectare hidrolitica: (1 – 5) – (4 – 5) – (2 – 3)**

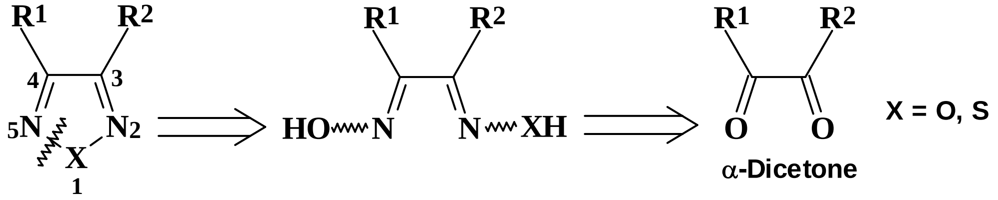


LG = halo, OH, OR
X = O, NH, NR, S

Nota 1: legatura ***N - N*** este **preformata**
Nota 2: triazolii *N* - substituiti care rezulta sunt regioizomerii **1*H*-1,3,4 !!**

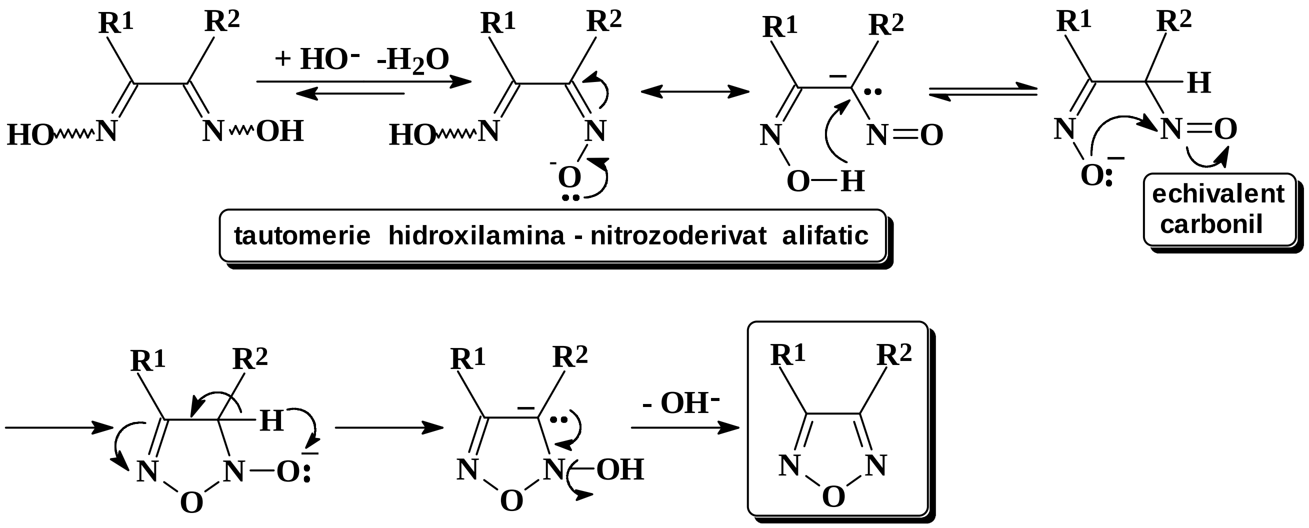
2.1.4. 1,2,5-Triheteroazoli

- deconectare hidrolitica: (1 – 5)



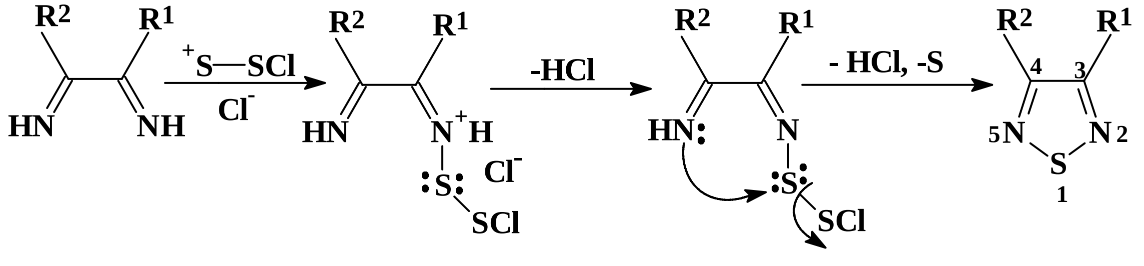
- deconectarea este **formala**, **strict necesara** fiind prezenta celor **doi atomi de azot** grefati si **functionalizati convenabil** pe scheletul α-dicetonei: **dioxime** sau **diimine**

Exemplul 1: 1,2,5-oxadiazoli din dioxime vicinale

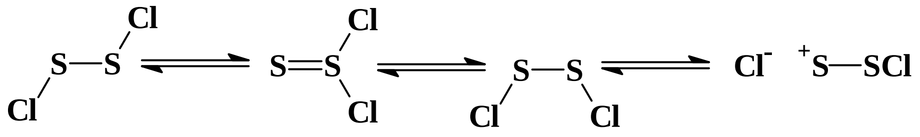


Nota 1: problema **diastereomeriei *E* – *Z*** a dioximelor vicinale se rezolva prin co-existenta **tautomeriei** hidroxilamina – nitrozo derivat alifatic (**cataliza bazica**)
Nota 2: cataliza acida ar putea conduce la **hidroliza** oximelor
Nota 3: metoda nu se preteaza pentru introducerea secventei de atomi **=*N*-*N*(R)-*N*=**

Exemplul 2: 1,2,5-tiadiazoli prin tionarea diiminelor vicinale



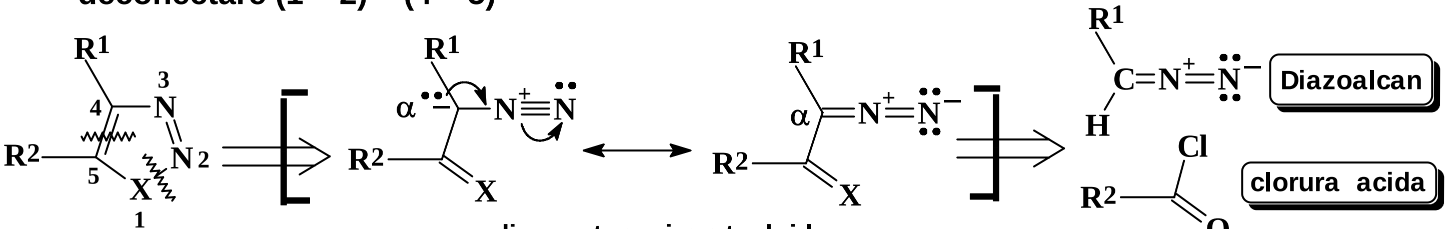
Nota 1: se utilizeaza un agent de tionare tipic (si util prin instabilitatea lui) **clorura de sulf S_2Cl_2**



2.2. Sinteze din precursori care admit deconectari *retro* Diels – Alder si similare

2.2.1. Triheteroazoli: 1,2,3-tiadiazoli si 1*H*-1,2,3-triazoli

- **deconectare (1 – 2) – (4 – 5)**

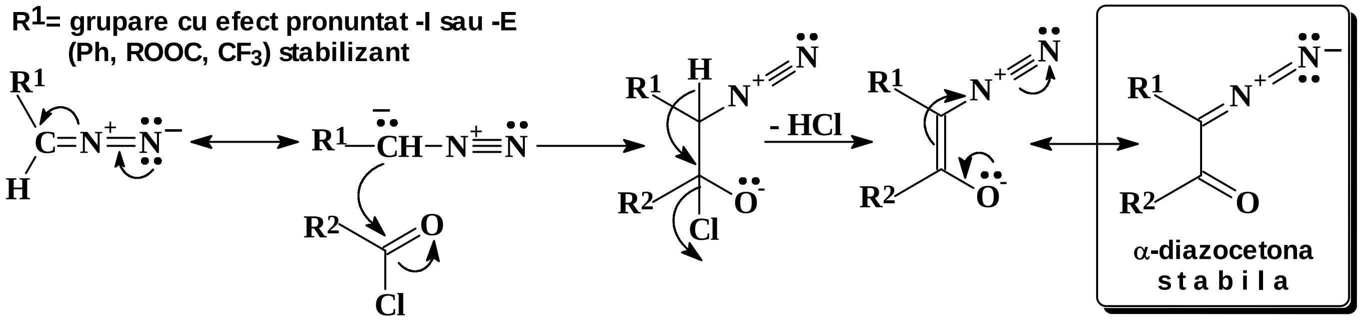


α-diazocetona, instabila
pentru X = S, NH, NR

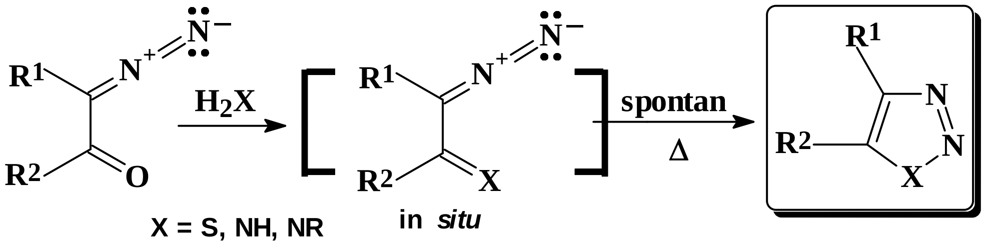
Exemplu:

- **prepararea α - diazocetonei:**

R1= grupare cu efect pronuntat -I sau -E
(Ph, ROOC, CF3) stabilizant

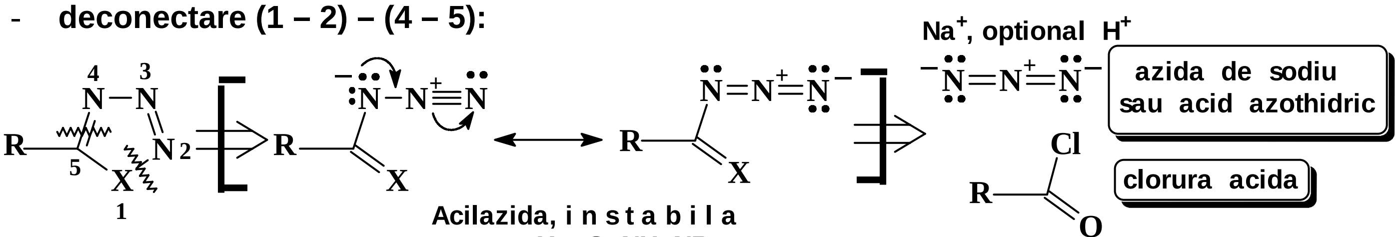


- **ciclizarea spontana (vezi tautomeria inel – catena):**



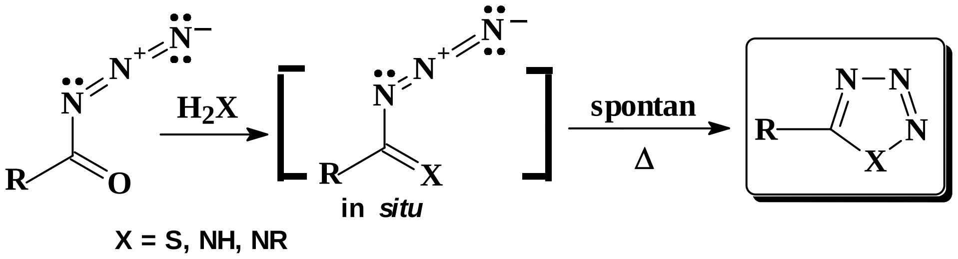
2.2.2. Tetraheteroazoli: 1,2,3,4-tiatriazoli si 1,2,3,4-tetrazoli (1*H* si 2*H*)

- **deconectare (1 – 2) – (4 – 5):**



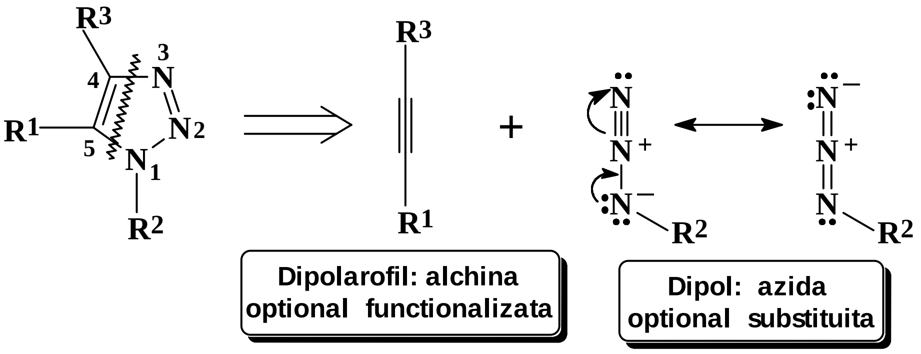
Acilazida, instabila
pentru X = S, NH, NR

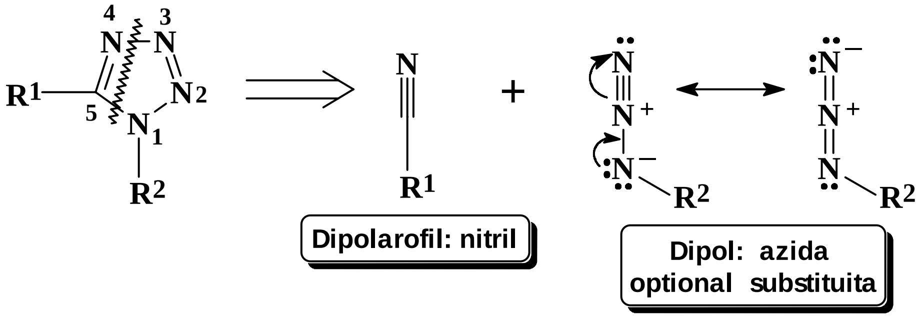
$$NaN_3 + R\text{-}CO\text{-}Cl \longrightarrow R\text{-}CO\text{-}N_3 + NaCl$$



2.2.3. 1*H*-1,2,3-Triazoli si 1*H*-1,2,3,4-tetrazoli prin cicloaditii [4 + 2] 1,3-dipolare

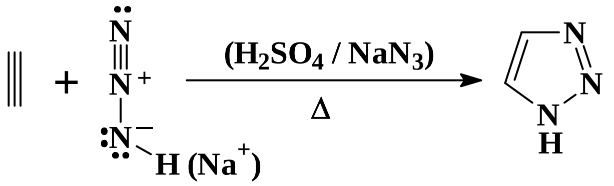
- **deconectare (1 – 5) – (3 – 4):**





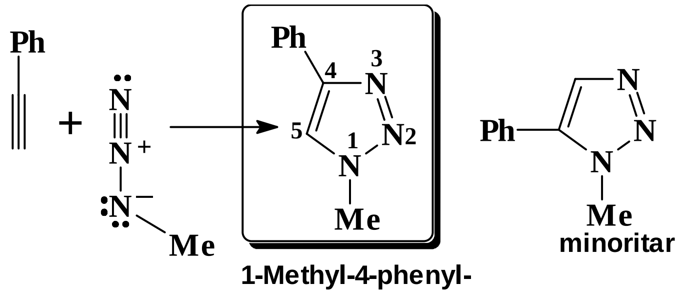
Exemplul 1:

- **1*H*-1,2,3-triazolul, ca atare:**



Exemplul 2:

- **ciclizare regioselectiva:**

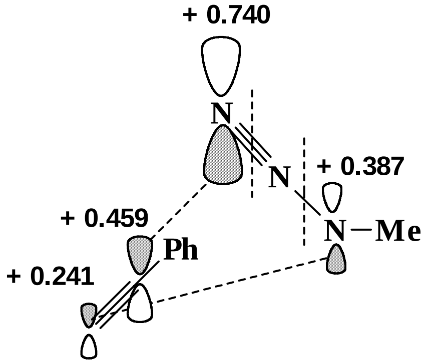


**1-Methyl-4-phenyl-
-1*H*-1,2,3-triazole
MAJORITAR**

Identificarea orbitalilor stereodirectori:

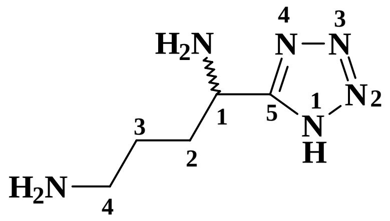
Energii OMF (β)	HOMO	LUMO	
Fenilacetilena	**+ 0.836**	- 0.775	donor
Metilazida	+ 0.982	**- 0.302**	acceptor

$$\text{min. } \Delta E_{LUMO\ -\ HOMO} = -0.302 - (+0.836) = -1.138\ \beta$$



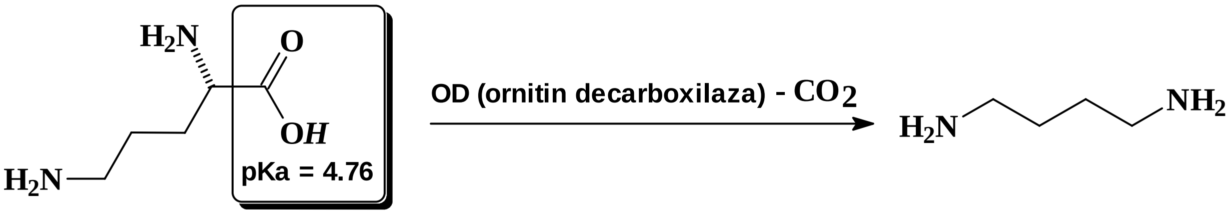
Exemplu de utilizare a cicloaditiei [4 + 2] 1,3 – dipolare la prepararea unui inlocuitor bioizosteric

(SmithKline Beecham Pharmaceuticals®)

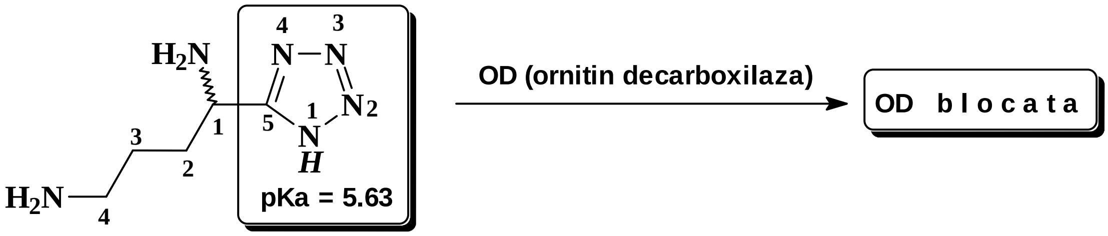


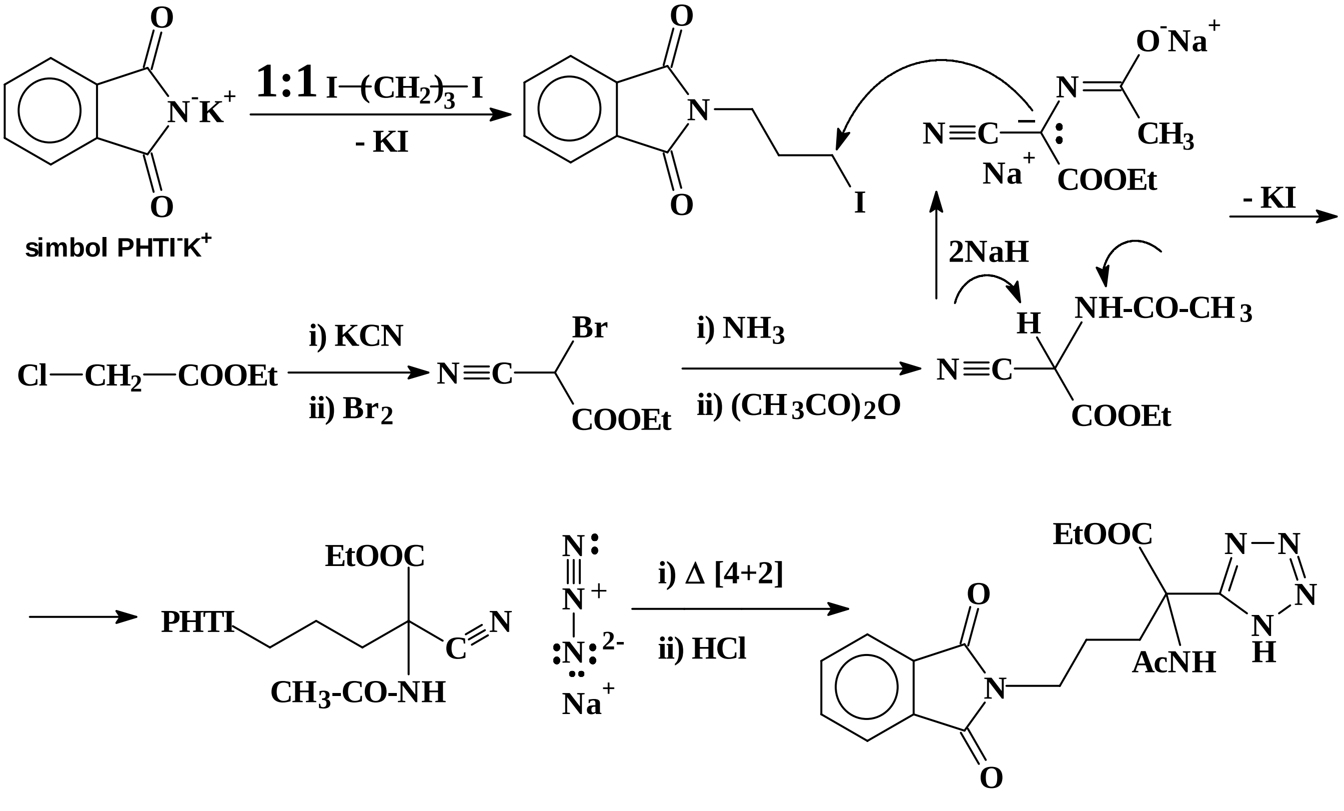
rac-5-(1,4-Diaminobutane-1-yl)-1*H*-1,2,3,4-tetrazole

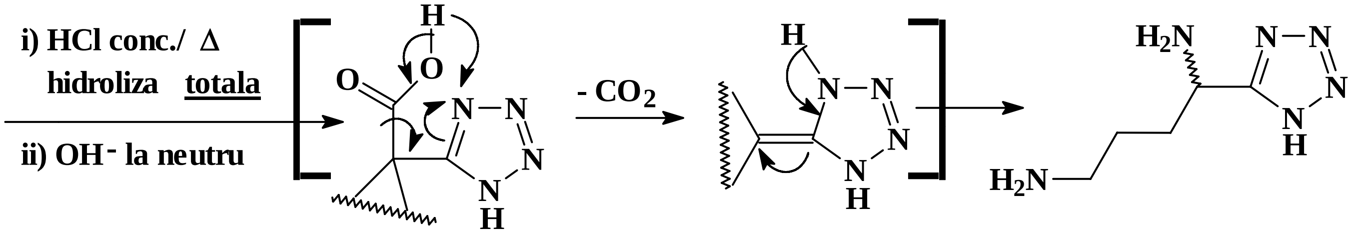
- problema: prepararea unui **inlocuitor al ornitinei** cu arhitectura moleculara **similara, acceasi aciditate** dar **nedecarboxilabil**



ORNITINA





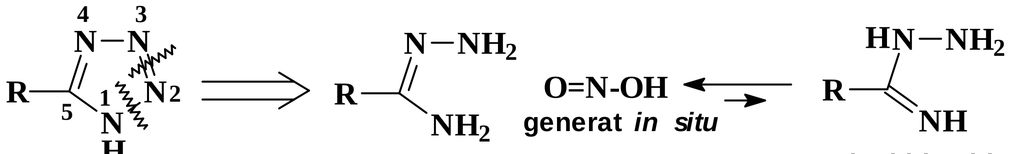


tetrazolul asista α - decarboxilarea

2.3. Sinteze particulare de tetraheteroazoli

2.3.1. 1*H*-1,2,3,4-Tetrazoli *C* – 5 substituiti *via* diazotare

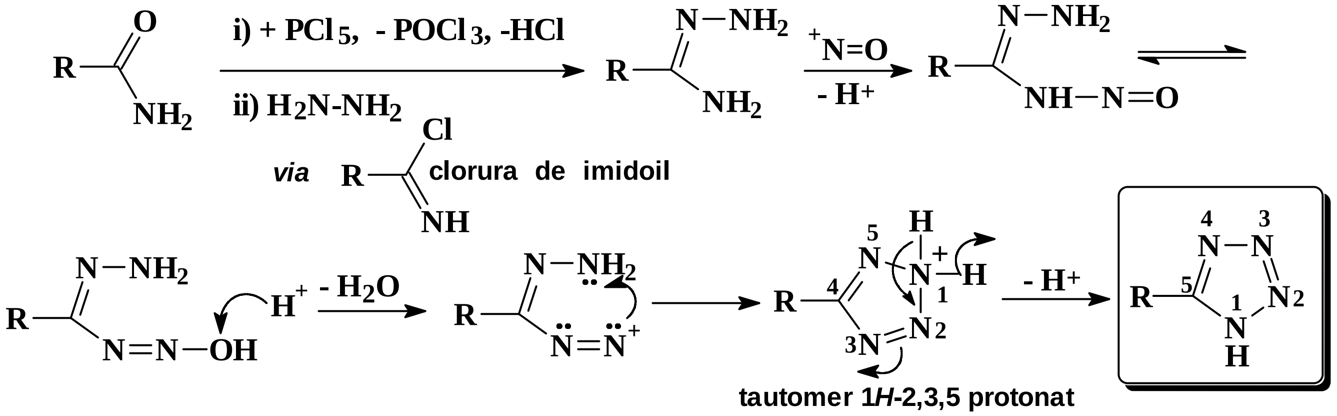
- deconectare: (1 – 2) – (2 – 3)



Amidohidrazona

Iminohidrazide

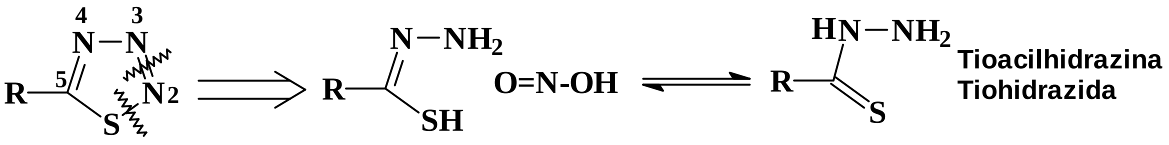
$HNO_2 + H^+ \rightleftharpoons {}^+N=O + H_2O$



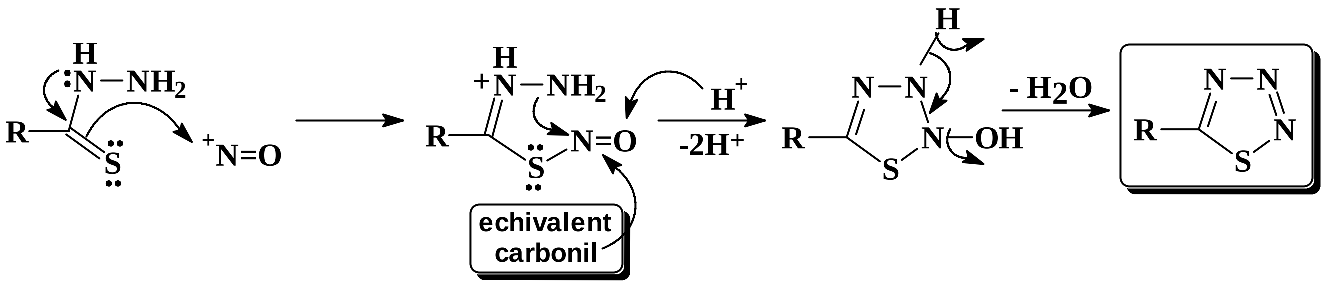
tautomer 1*H*-2,3,5 protonat

2.3.2. 1,2,3,4-Tiatriazoli *C* - 5 substituiti *via S* – nitrozare

- deconectare: (1 – 2) – (2 – 3)



Tiolhidrazona



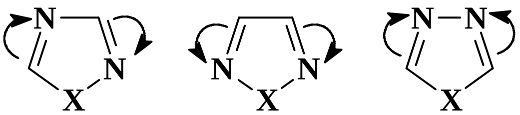
Nota: a se compara cu **efectul catalitic al tioureii** in reactiile de **diazotare**

3. Functionalizarea superioara

3.1. Functionalizarea prin substitutie electrofila

3.1.1. Functionalizarea prin substitutie electrofila la *C* heterociclic

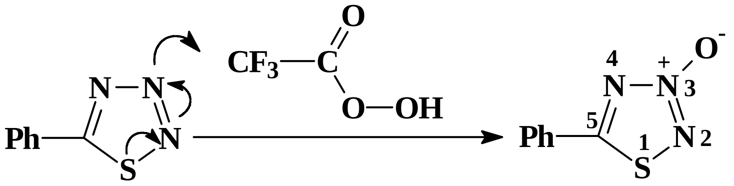
- prezinta **importanta minora** din cauza efectului combinat **dezactivant** al **celor doi** atomi de **azot piridinici**



3.1.2. Functionalizarea prin atac electrofil la azot

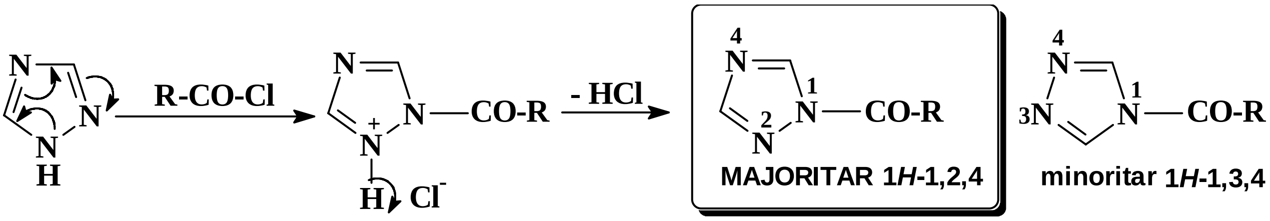
- are loc, de regula regioselectiv, la *N*-piridinici
- reactiile sunt mai putin raspandite si aplicate, fata de 1,3- si 1,2- azoli din cauza bazicitatii mai reduse a azolilor cu 3,4 heteroatomi.

Exemplul 1: *N* – oxidarea

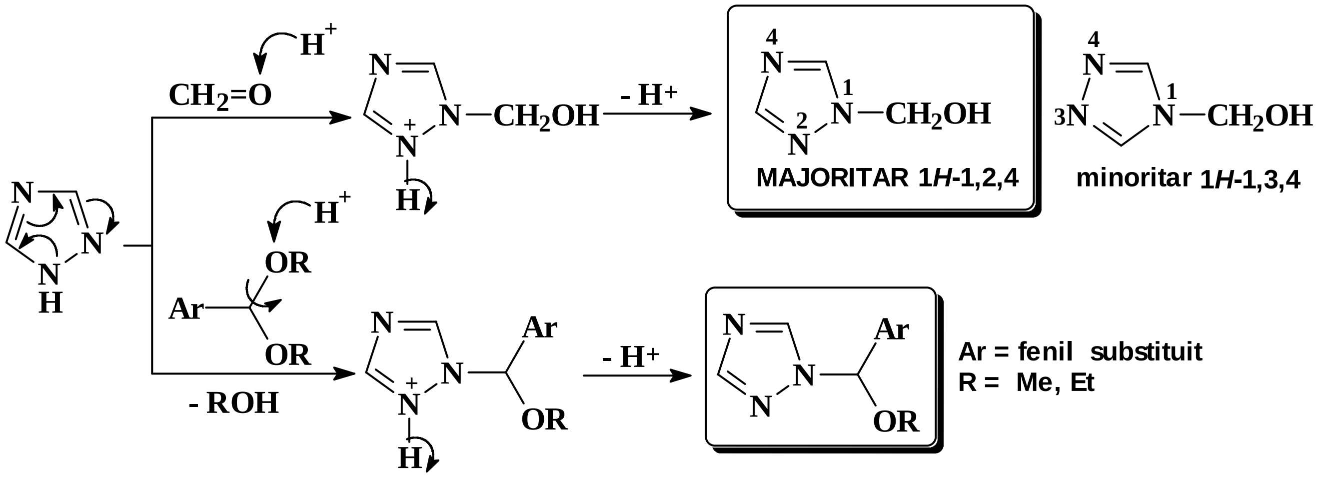


5-Phenyl-1-thia-2,3,4-triazole-3-oxyde

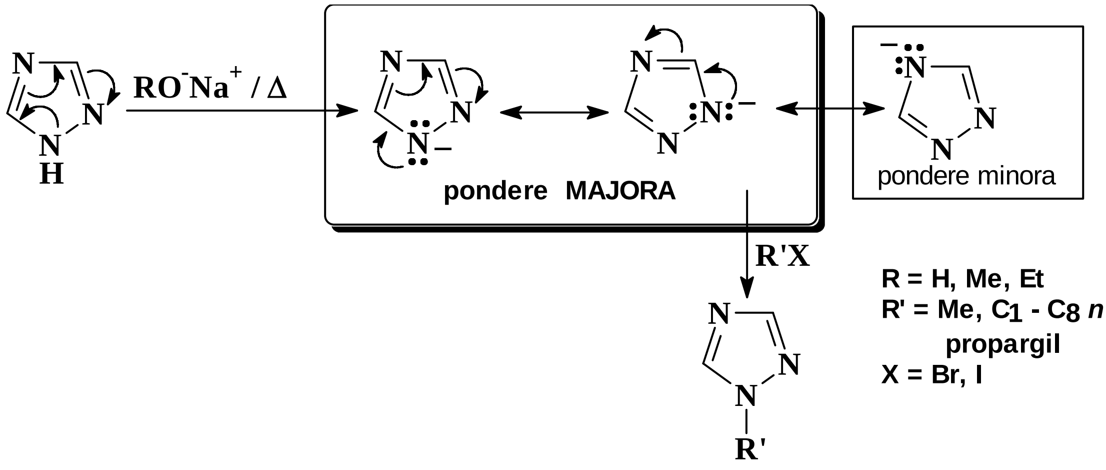
Exemplul 2: *N* – acilarea



Exemplul 3: reactii de tip Mannich



Exemplul 4: in cazul **anionilor** rezultati prin ***N* - deprotonare** se mentin aceleasi regioselectivitati, desi problema azotului piridinic dispare

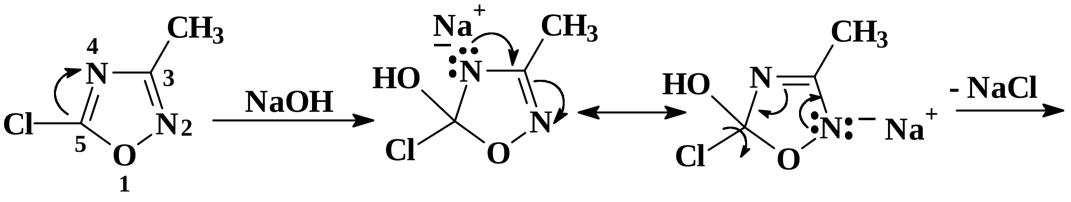


R = H, Me, Et
R' = Me, C_1 - C_8 *n* - alchil, allil propargil
X = Br, I

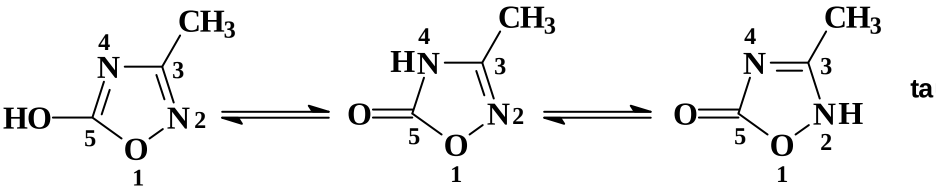
3.2. Functionalizarea prin substitutie nucleofila

- se refera mai ales la **substituirea halogenilor** din secventa **–C(*Hal*)=** iar atomul de carbon este **adiacent** la **doi** heteroatomi
- substraturile halogenate se comporta adesea ca si **halogenuri acide mascate** (cloruri acide, cloruri de imidoil, etc.) din seria alifatica
- la limita, unele structuri halogenate sunt instabile fata de umiditate
- nucleofili: **R-OH**, **R-O⁻**, **Ar-O⁻**, amine, etc.

Exemplul 1:

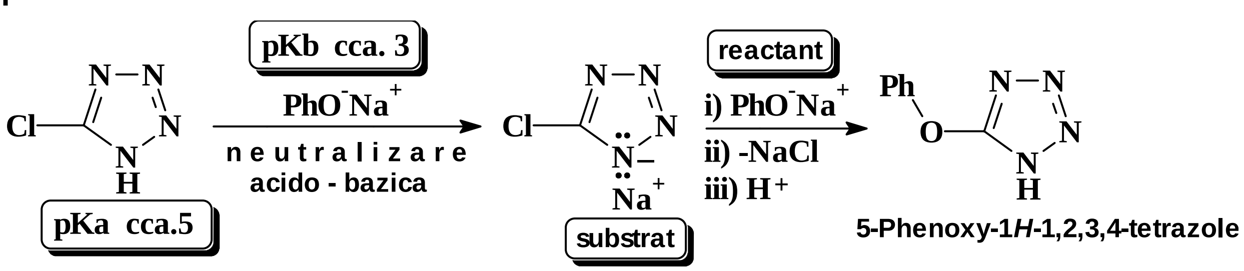


5-Chloro-3-methyl-1-oxa-2,4-diaz ole
5-Chloro-3-methyl-1,2,4-oxadiaz ole



5-Hydroxy-3-methyl-1-oxa-2,4-diazole | **3-Methyl-(4*H*)-1,2,4-oxadiazoline-5-one** | **3-Methyl-(2*H*)-1,2,4-oxadiazoline-5-one**

Exemplul 2:



5-Phenoxy-1*H*-1,2,3,4-tetrazole

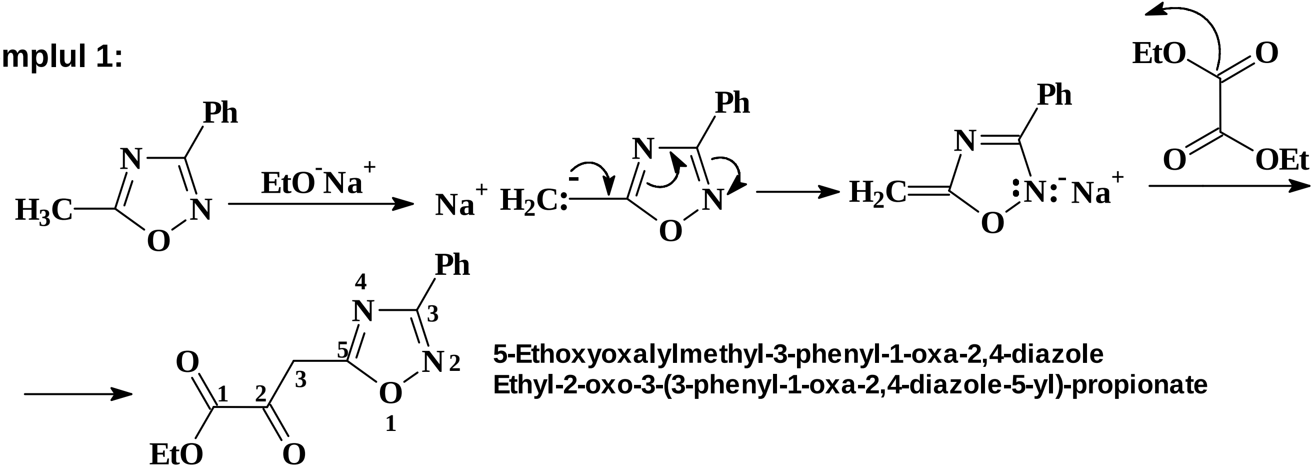
Nota: atomul de clor, desi grefat pe o structura anionica delocalizata, **ramane labilizat** de catre secventa de **patru azaatomi** ⁻N⁻–N = N – N =

3.3. Functionalizarea prin metalare

Generalitati:

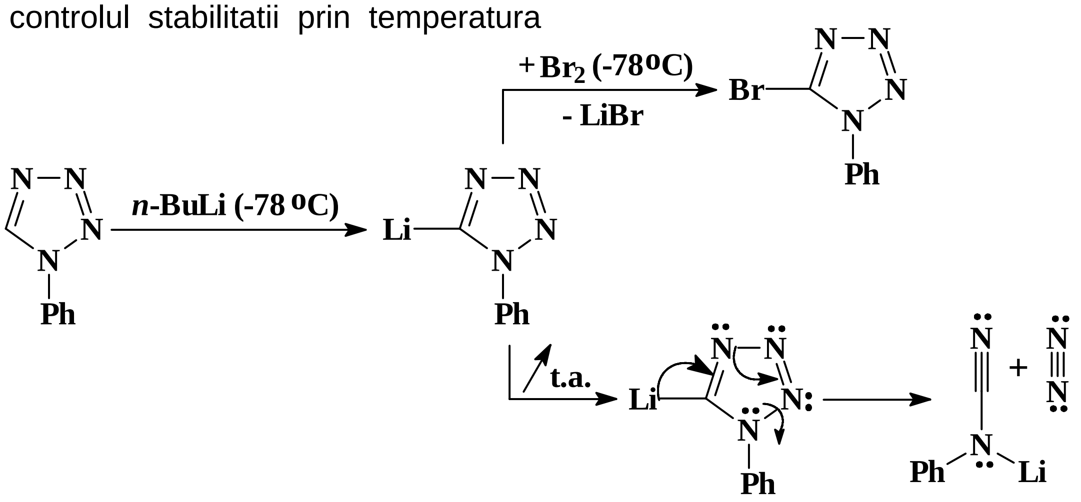
- datorita numarului dominant de heteroatomi fata de carbon in heterociclu, deprotonarea la **–C*H*= se realizeaza mai usor** dar produsii rezultati **nu sunt stabili in anumite cazuri.**
- **grupele metil** grefate direct pe heterociclu **in pozitie dublu adiacenta** fata **de doi heteroatomi** sunt **deprotonabile** chiar **cu baze mai slabe decat *n*-BuLi**
- **metalarile au mare valoare preparativa**

Exemplul 1:



5-Ethoxyoxalylmethyl-3-phenyl-1-oxa-2,4-diazole
Ethyl-2-oxo-3-(3-phenyl-1-oxa-2,4-diazole-5-yl)-propionate

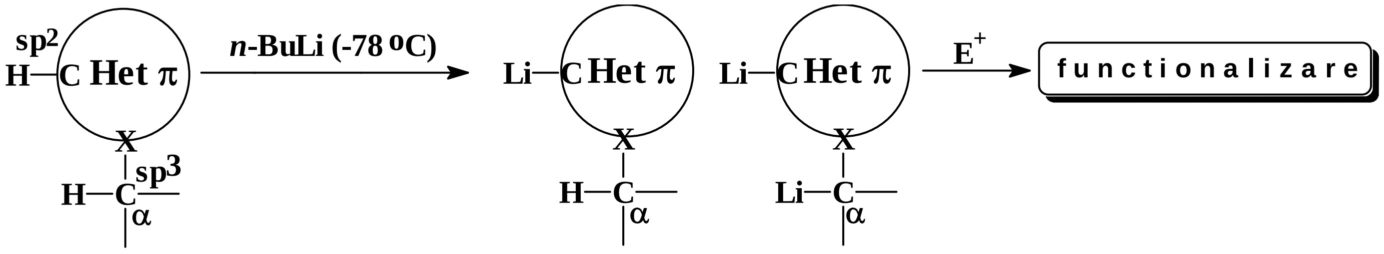
Exemplul 2: controlul stabilitatii prin temperatura



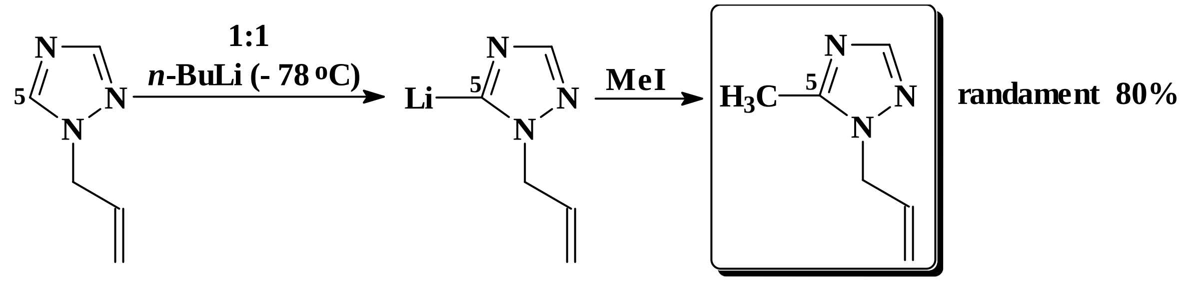
Exemplul 3: stabilizarea concurentiala a carbanionilor de tip sp^2 si sp^3 de catre unii 1*H*-1,2,4 triazoli *N* – substituiti

Problema: daca un carbon hibridizat **sp^3** aflat in pozitie α **fata de un heteroatom** dintr-un heterociclu poate genera carbanioni la concurenta:

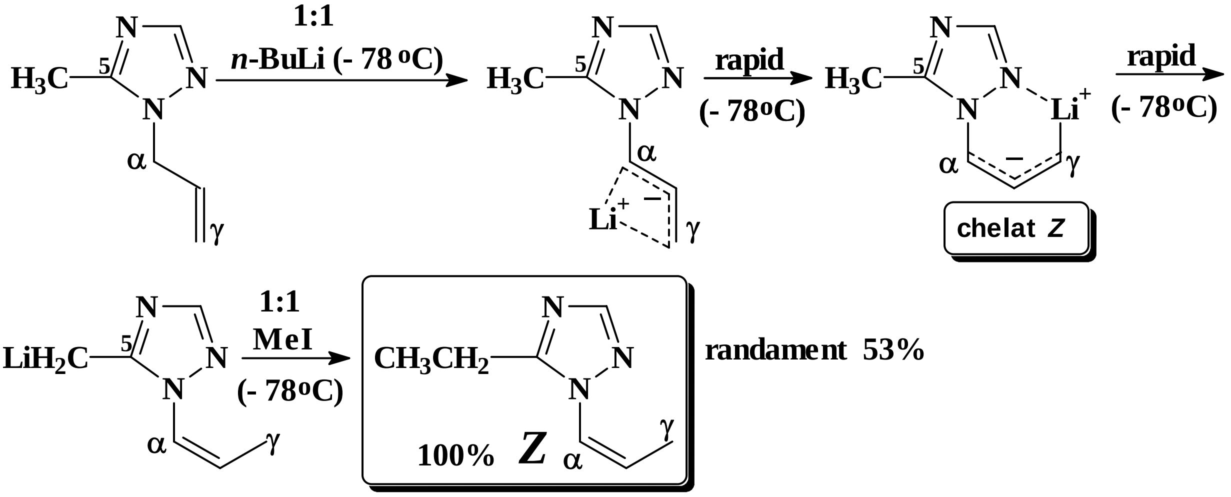
a) cu un carbon hibridizat **sp^2 apartinand** heterociclului.
b) cu un carbon hibridizat **sp^3 direct legat** de un carbon heterociclic



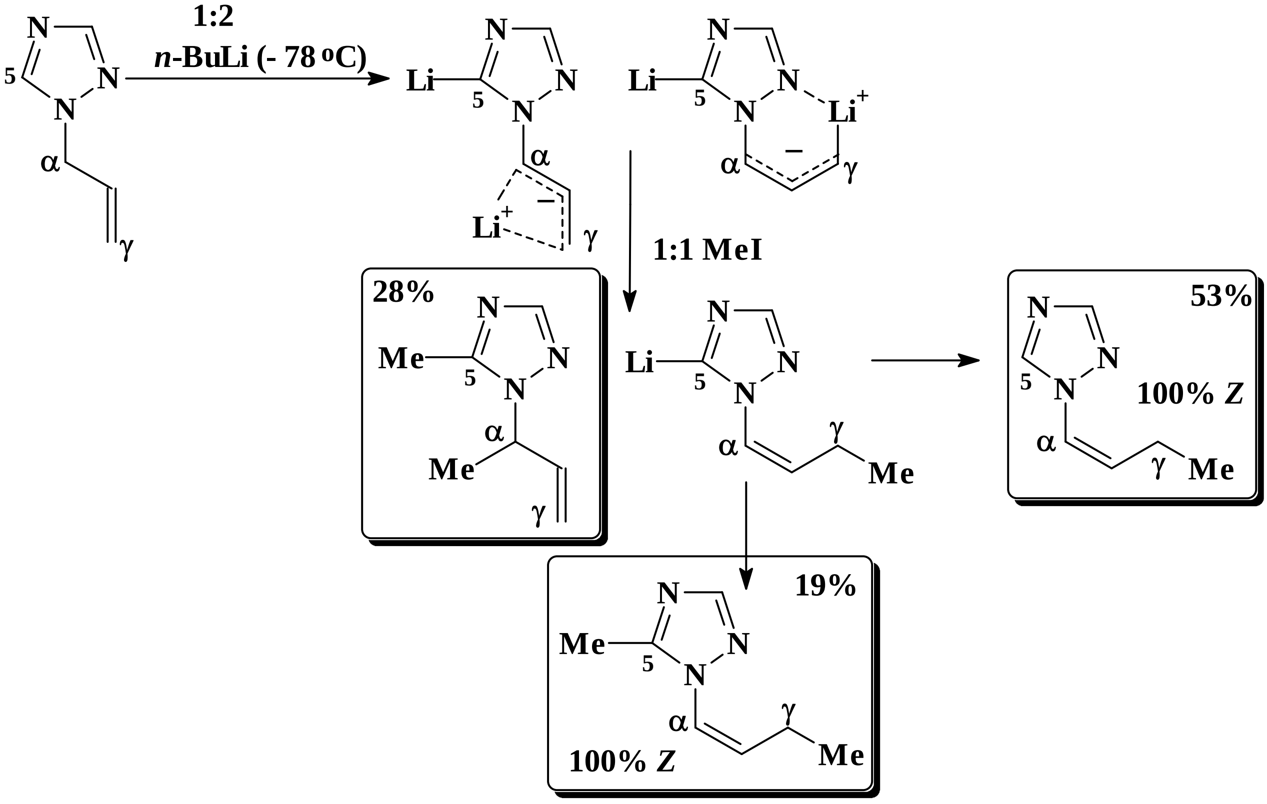
a) orientarea uzuala a metalarii la *C*-5, dublu adiacent la doi heteroatomi



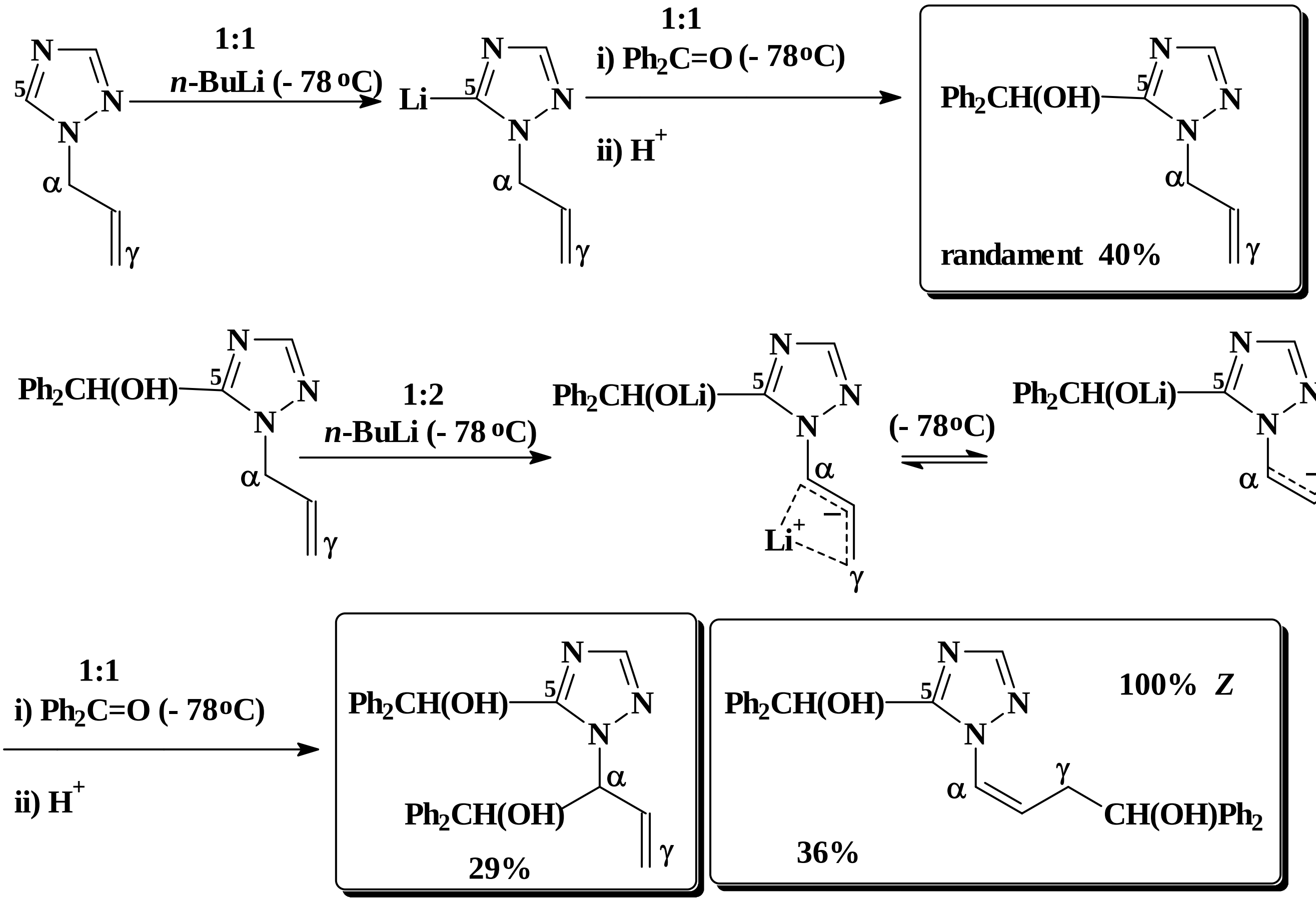
b) transpozitia alilica $\alpha \rightarrow \gamma$ a α- carbanionului si reorientarea metalarii la *C*-5 de catre o forma chelata configurata *Z*:



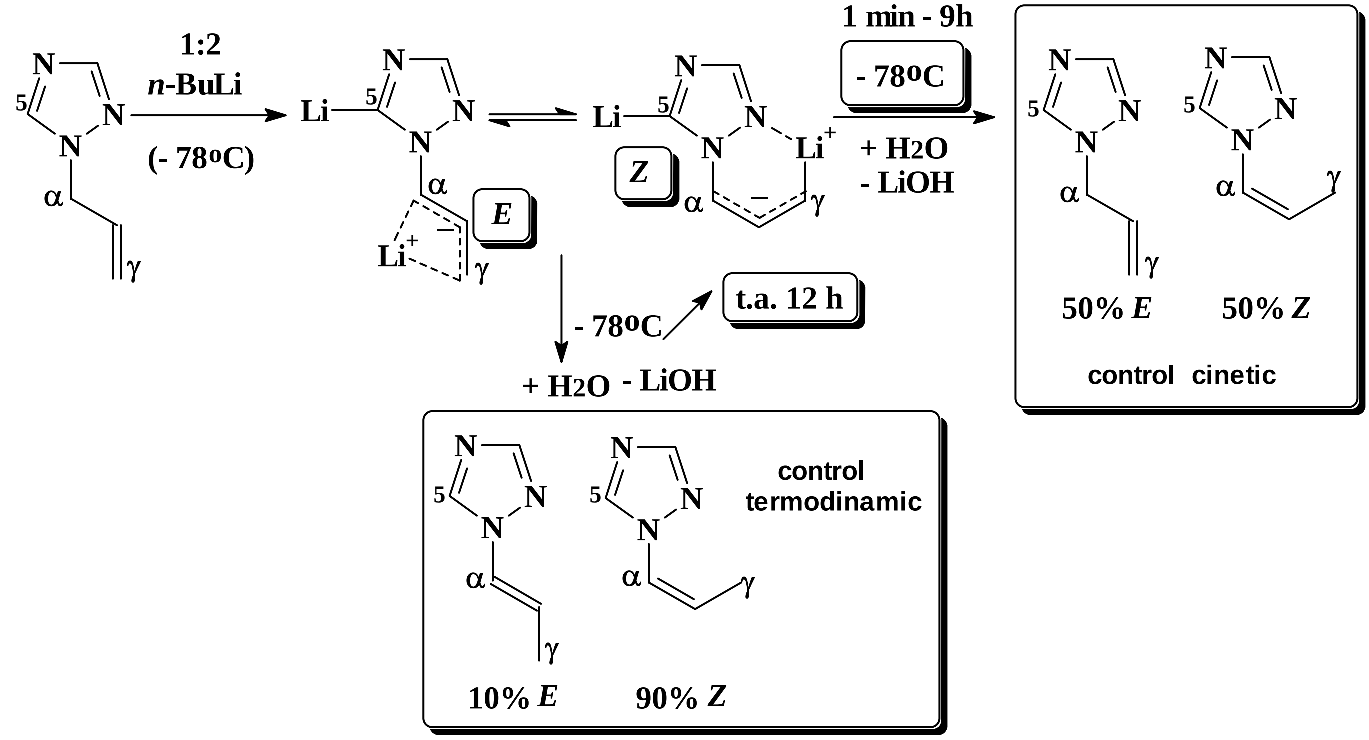
c) concurenta electrofila intre pozitiile C-5, α si γ



c) transpozitia alilica $\alpha \rightarrow \gamma$ a α- carbanionilor in cazul unui electrofil voluminos:



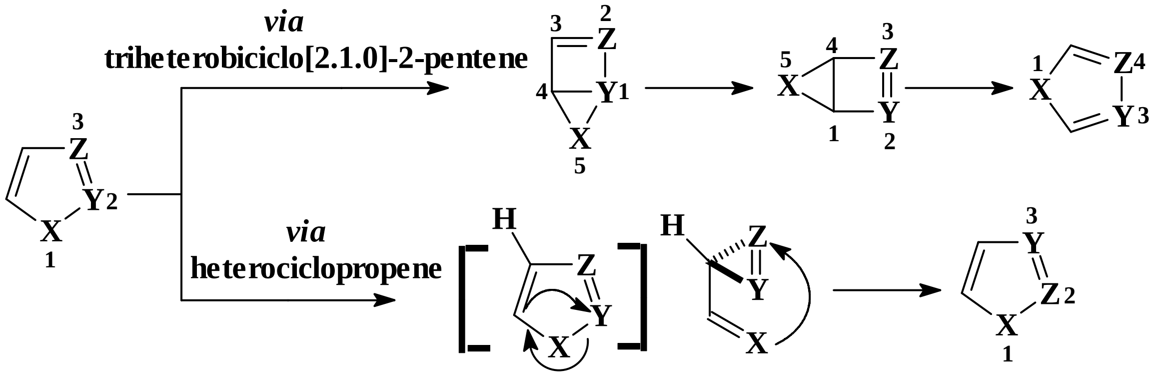
d) echilibrarea carbanionilor dilitiati ai 1*H*-1,2,4-triazolului; controlul cinetic si termodinamic.



3.4. Procese fotochimice:

3.4.1. Transpozitii:

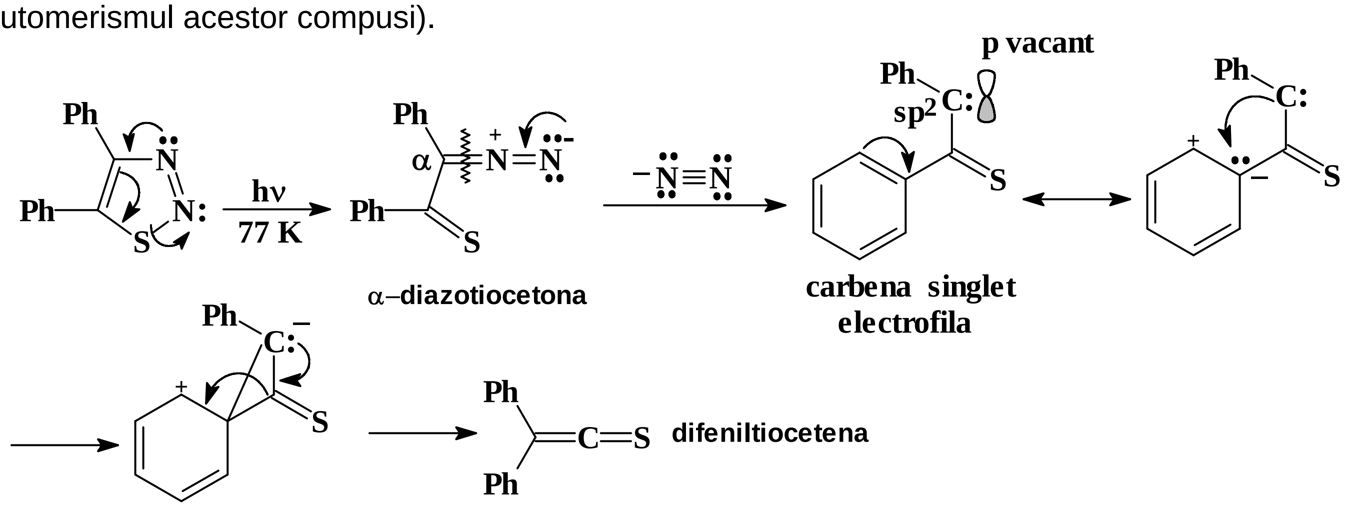
- sunt **procese frecvente** pentru azolii cu **trei heteroatomi** in **secventa 1,2,3**
- rezultatul acestor transpozitii, **fara importanta preparativa**, duce la obtinerea de regioizomeri 1,2,3 sau 1,3,4.
- sunt cunoscute **doua** mecanisme principale:



3.4.2. Fragmentari:

- sunt uzuale si raspandite pentru azolii cu mai multi heteroatomi
- varianta fotochimica evita efectuarea reactiei la temperaturi exagerat de ridicate
- uneori, **intermediari instabili** rezultati din fragmentare pot fi captati prin **cicloaditii**

Exemplul1: fragmentarea fotochimica a unor 1-tia-2,3-diazoli 4,5-disubstituiti (vezi *ring – chain* tautomerismul acestor compusi).



Exemplul 2: fragmentarea 1-tia-2,3-diazolului *ca atare*; captarea intermediarului prin cicloaditie in scopul dovedirii mecanismului