PENTAHETARENES WITH ONE HETEROATOM

1. General

2. Syntheses

a) *Knorr – Paal* methodology
b) *Knorr* methodology

3. Direct functionalisation

3.1. Functionalisation by electrophilic substitution

3.1.1. Common reactions of all systems

a) *Vilsmeier-Haak* formylation
b) *Mannich* reaction
c) Sulfonation and nitration
d) *Friedel & Crafts* reaction
e) (Poly)condensation with electrophiles of type carbonyl
f) Higher functionalisation by electrophilic substitution
g) Proton as electrophile

3.1.2. Functionalisation *via* metallation

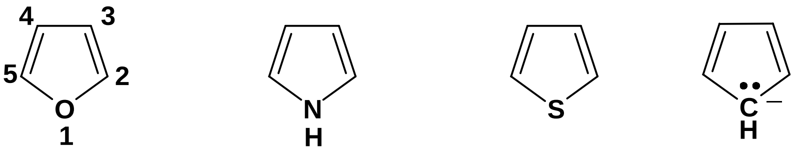
a) Pyrrole functionalisation *via* metallation
b) Functionalisation *via* lithiation

3.1.3. Photochemical rearrangements

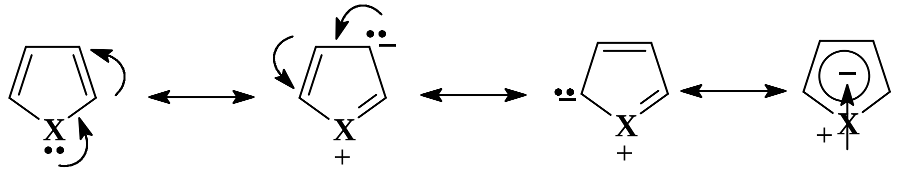
Modifications (improvements, additions, corrections, up to dates *etc.*) are subjected to no notice.

HETARENE PENTAATOMICE CU UN SINGUR HETEROATOM

1. Generalitati:

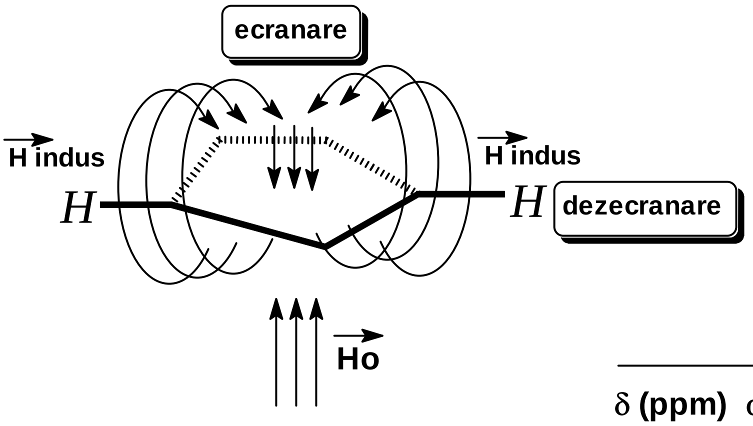


	ox <u>OL</u> **furan** **ox <u>A</u>**	**az <u>OL</u>** **pirol** **az <u>A</u>**	**ti <u>OL</u>** **tiofen** **ti <u>A</u>**	**anion ciclopentadienil**
Electronegativitate heteroatom (eV)	3.4	3.0	2.6	
Energie de conjugare (kcal / mol)	22	24	28	40

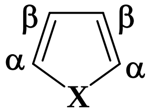


momentul dipolar global (Debye) : **0.70 (X = O); 1.97 (X = NH); 0.63 (X = S)**

→ **SISTEME π EXCEDENTARE** **sisteme cu (4n+2) e_{π}**



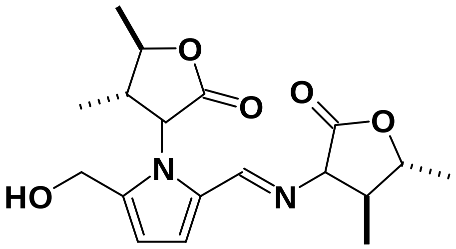
compusi diatropici

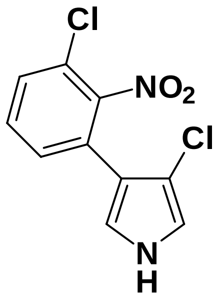


	X	O	NH	S
δ (ppm) α		7.40	7.19	6.62
δ (ppm) β		6.30	7.04	6.05

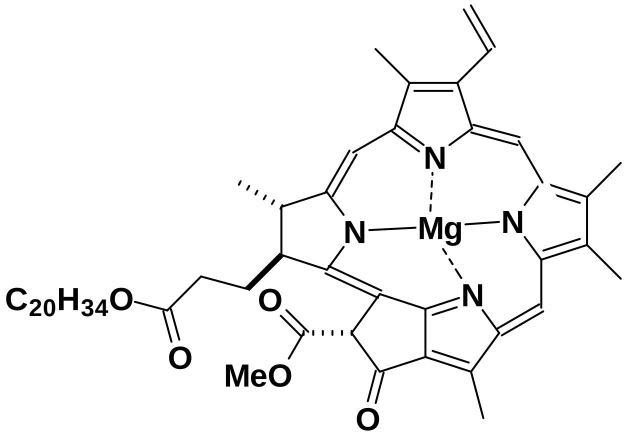
tipul de anizotropie in camp magnetic: **<u>diamagnetica;</u>** susceptibilitatea in camp magnetic: **<u>diamagnetica</u>**
Nota: pentru analogii cu **(4n) e_{π}** si anizotropia susceptibilitatea sunt **inversate** (**compusi paratropici**)

As natural products…

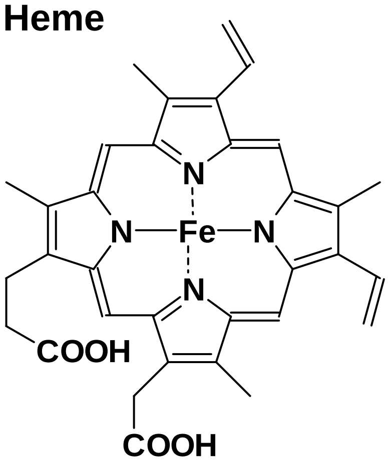


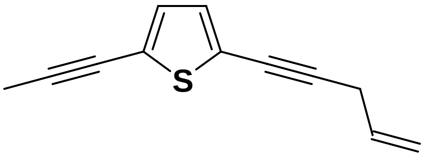


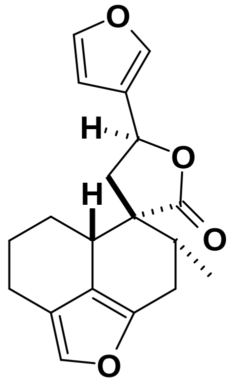
Chlorophyll



Heme

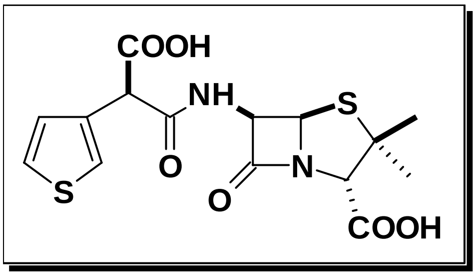




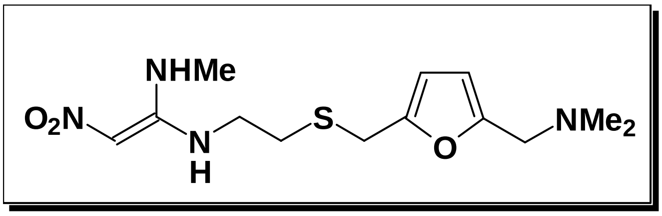


As drugs…

Penicillin

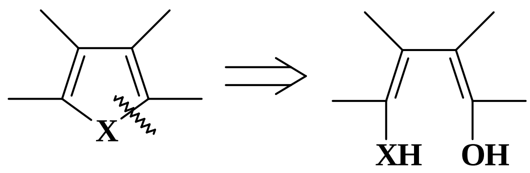


Against ulcer



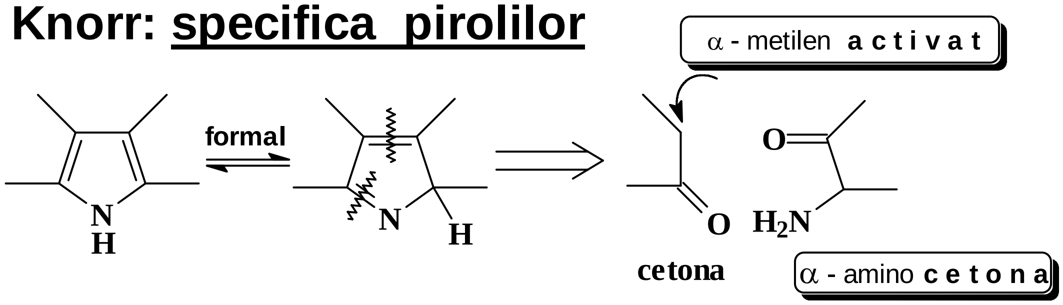
2. Sinteze:

Knorr & Paal

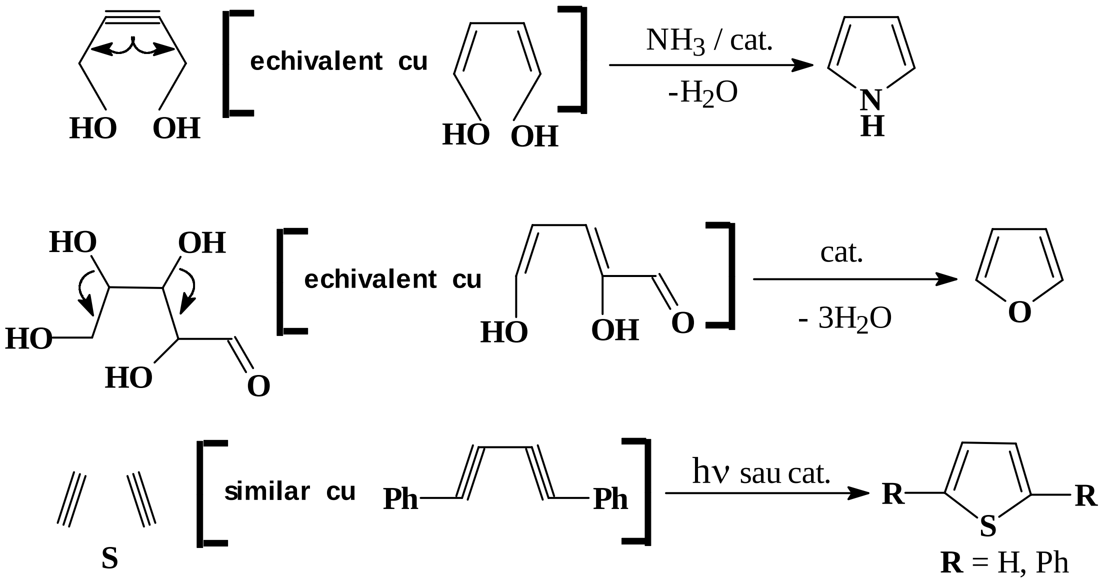


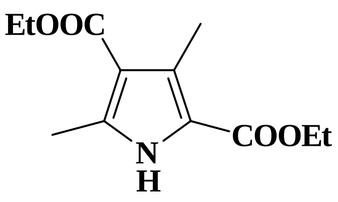
X = R-N; NH; O; S

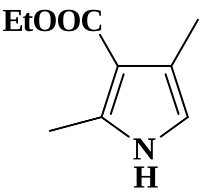
Knorr: specifica pirolilor

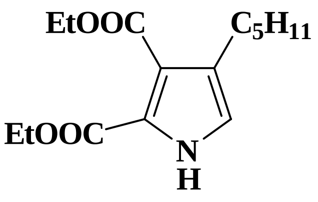


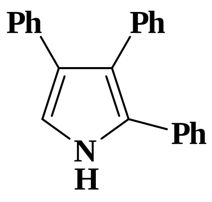
... si echivalenti (mascati) 1,4 - dicarbonilici



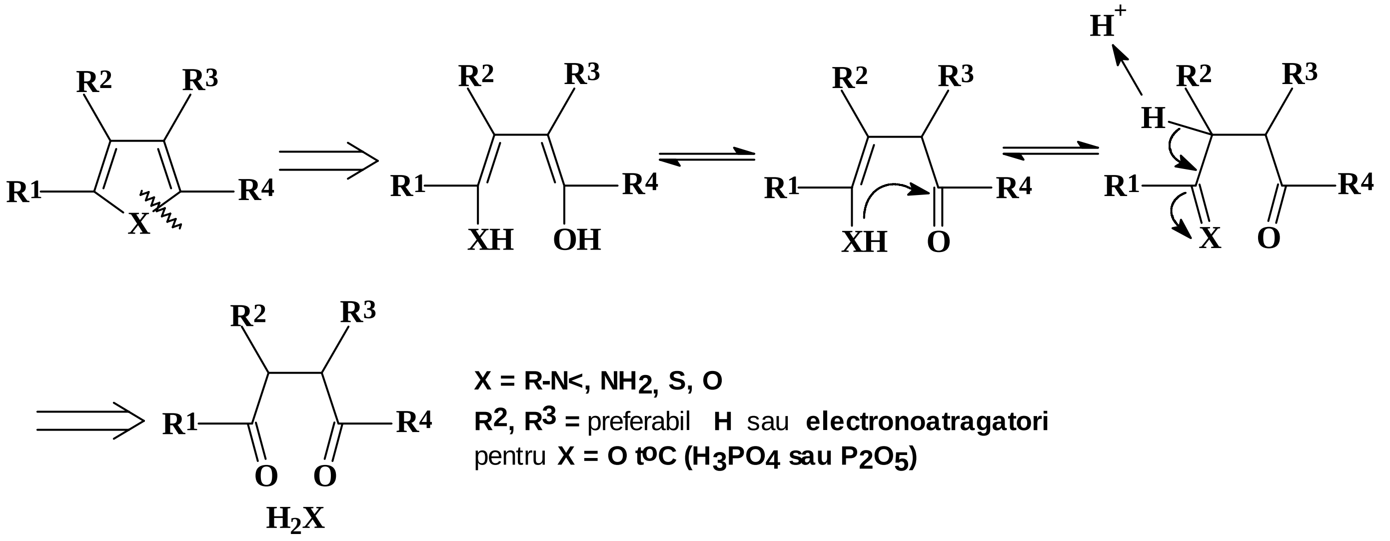




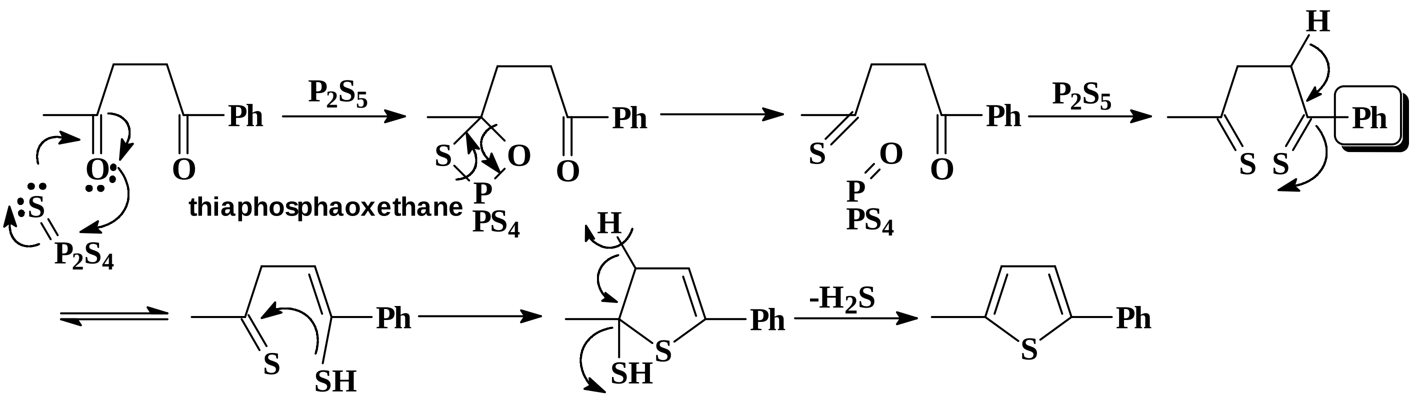




a) Metoda Knorr – Paal:

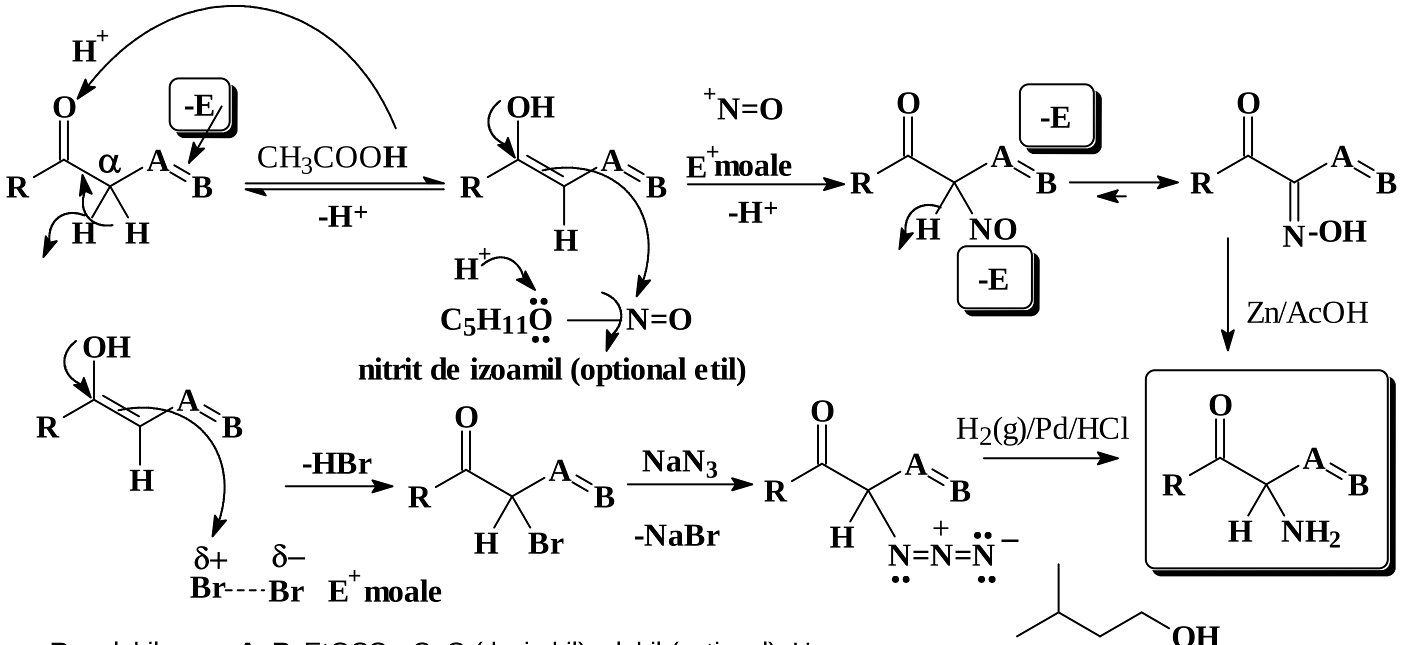


X = R-N<, NH$_2$, S, O
R^2, R^3 = preferabil **H** sau **electronoatragatori**
pentru **X = O t^{o}C (H$_3$PO$_4$ sau P$_2$O$_5$)**

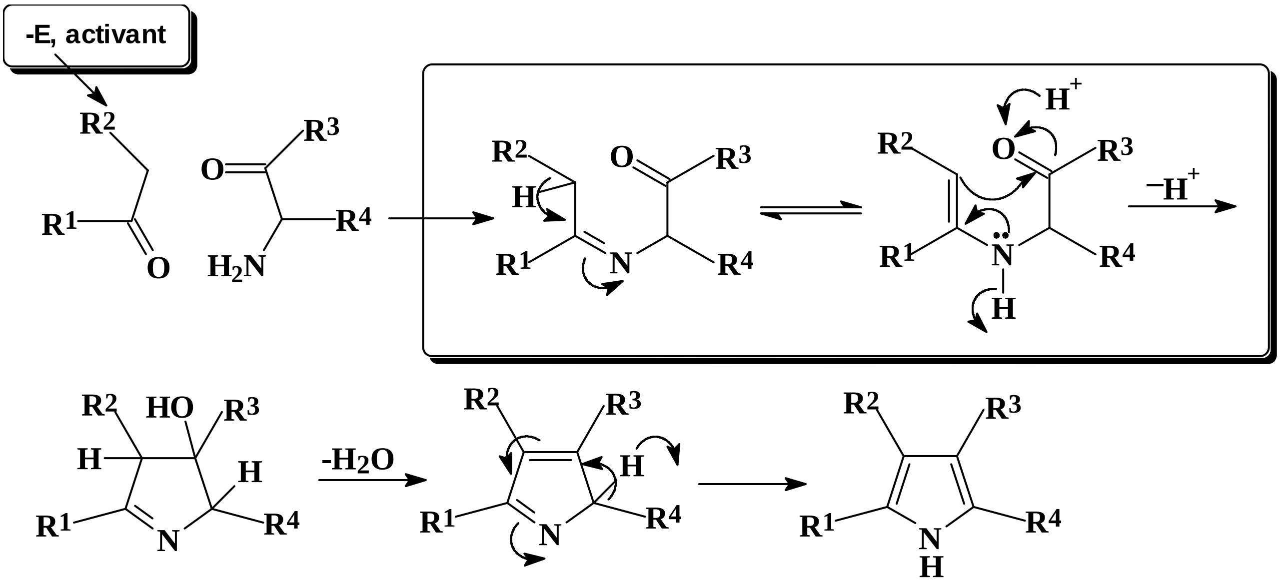


Nota 1: metoda este limitata de accesibilitatea **1,4-dicetonelor**
Nota 2: metoda **directa** de preparare a **sistemelor 2,5-disubstituite**
Nota 3: dialdehidele sunt **prea reactive** (condensare intermoleculara)

b) Metoda Knorr:

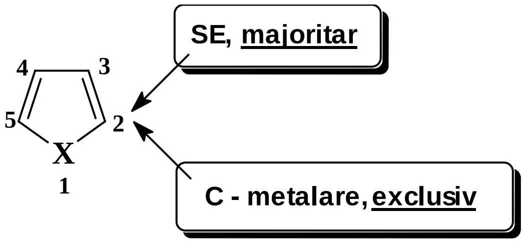


R = alchil **A=B:** EtOCO, -C=O (dezirabil), alchil (optional), H

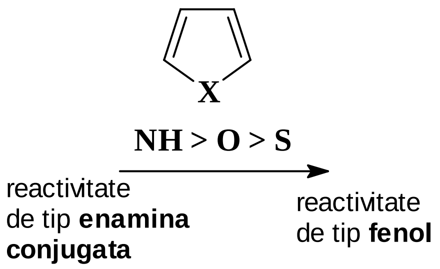


Nota: se prepara sisteme **3 (4) substituite,** ceea ce **nu este posibil,** in mod avanatajos, prin **functionalizare directa.**

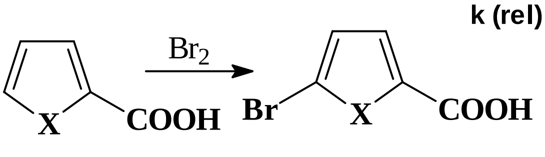
3. Functionalizarea directa:



3.1. Functionalizarea prin substitutie electrofila

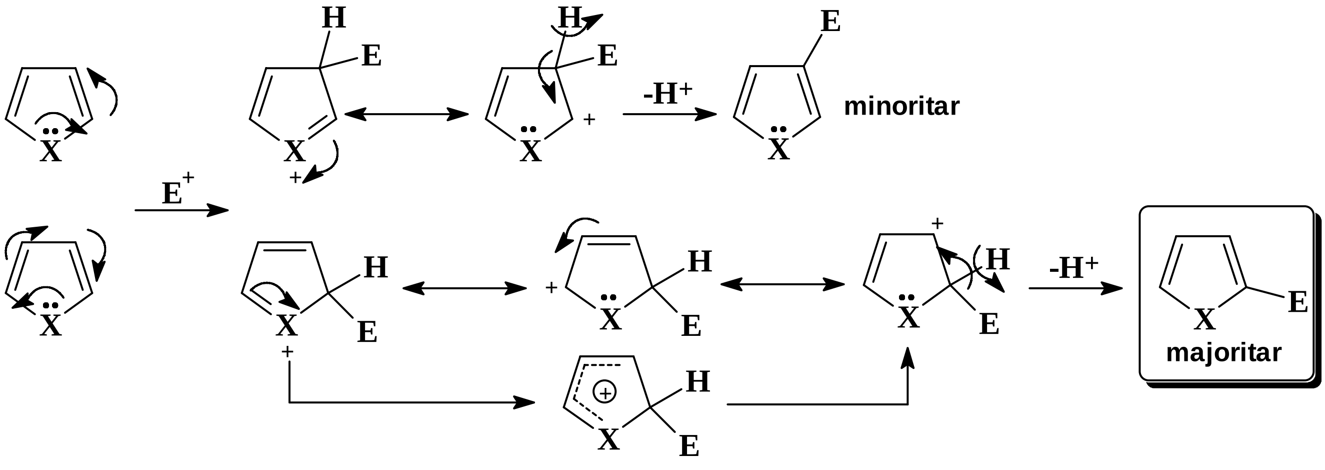


	NH	O	S
k (rel)	5.6×10^{8}	1.2×10^{2}	1.0

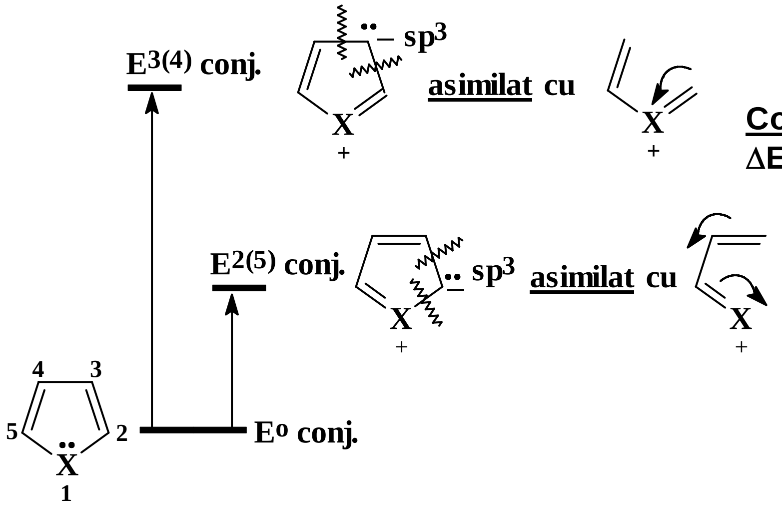


- sunt evitate conditiile **dure** de reactie (pentru acelasi gen de substitutie, sunt preferate variantele cu **electrofili moi**

- criteriu termodinamic:



-criteriu cinetic de apreciere a regioselectivitatii in reactiile SE

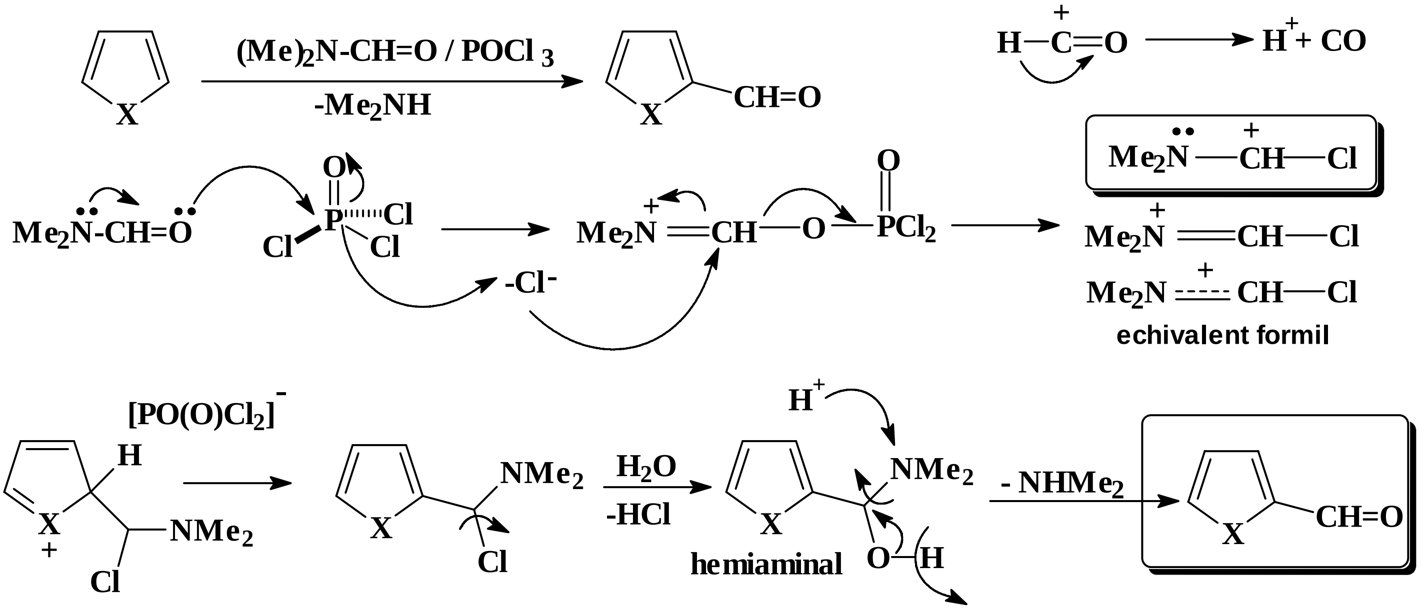


Concluzie:
$\Delta E = E^{o}$ conj. - $E^{2(5)}$conj < E^{o} conj. - $E^{3(4)}$conj.

Energia de localizare atomica la C-2(5) este mai mica decat energia de localizare atomica la C-3(4).

3.1.1. Reactii comune tuturor sistemelor:

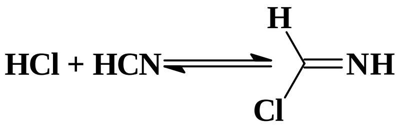
a) formilarea Vilsmeier & Haak: regioselectiva la C-2



alti echivalenti formil: $Me_2N\text{-}CH{=}O + CF_3\text{-}SO_2\text{-}O\text{-}SO_2\text{-}CF_3 \longrightarrow Me_2N\text{-}\overset{+}{C}H\text{-}O\text{-}SO_2\text{-}CF_3$

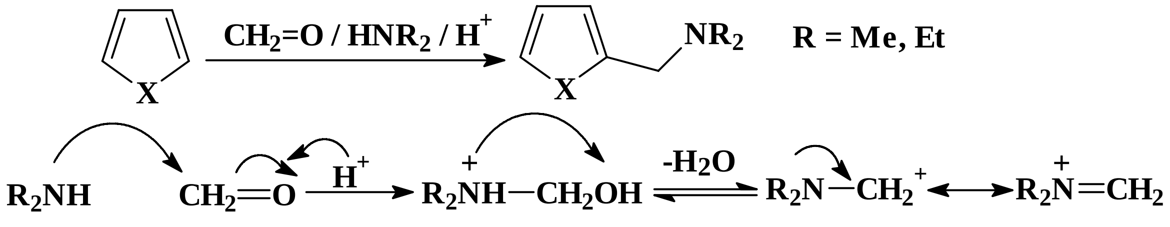
TfOH: $CF_3\text{-}SO_3H$ (Tf)$_2$O $CF_3\text{-}SO_2\text{-}O^-$ triflat

Nota: reactia este valabila sistemelor **heteroaromatice reactive**; are loc in conditii blande; in seria aromatica, pentru formilare cu rezultate similare, vezi **reactia Gattermann**



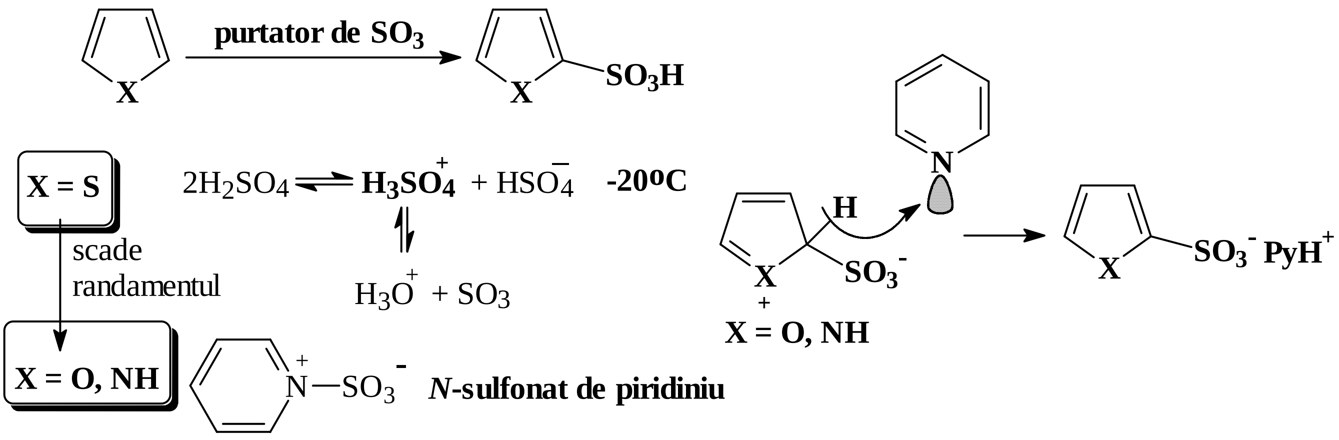
echivalent formil ca si clorura de imidoil a HCOOH

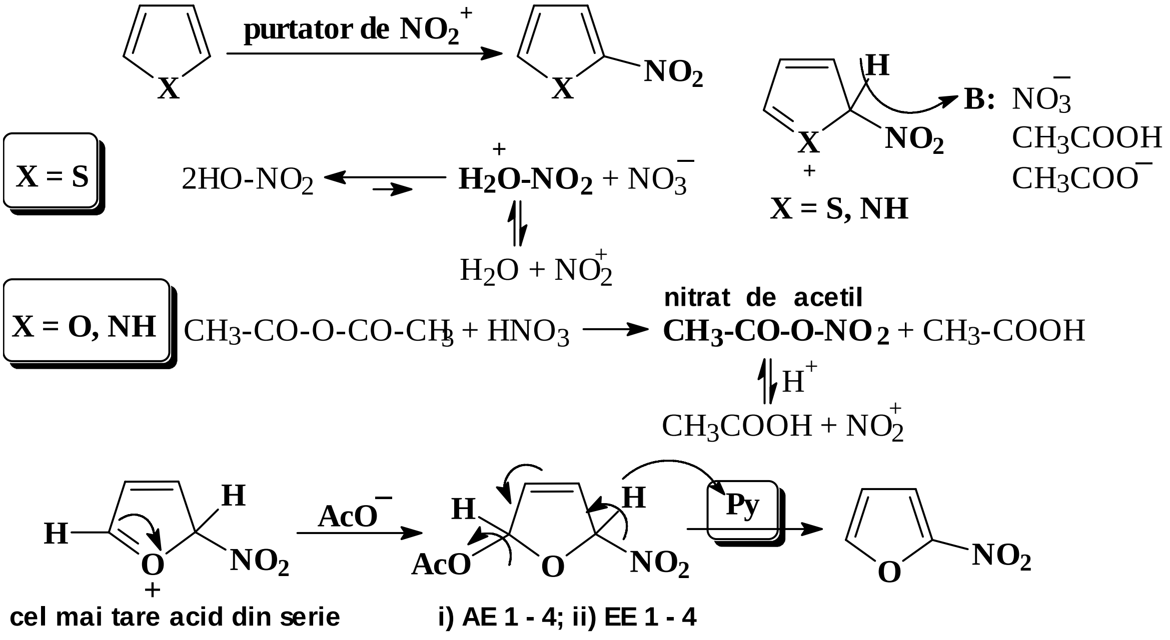
b) reactia Mannich: tipica



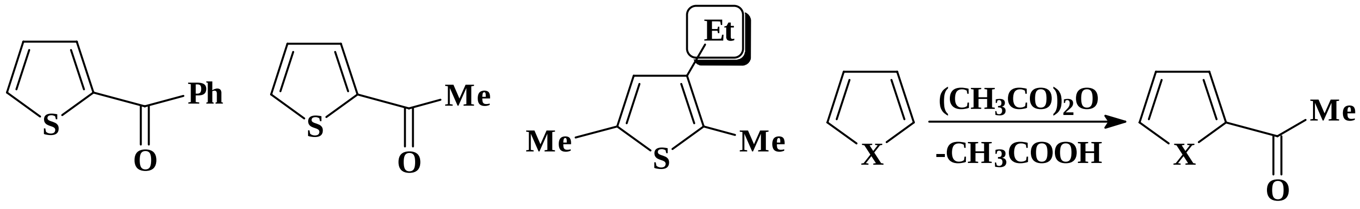
X = S (HCl); X = NH, O (AcOH)

C) "clasice (1)": sulfonarea si nitrarea (conditii blande)





d) “clasice (2)”: Friedel & Crafts (conditii blande)

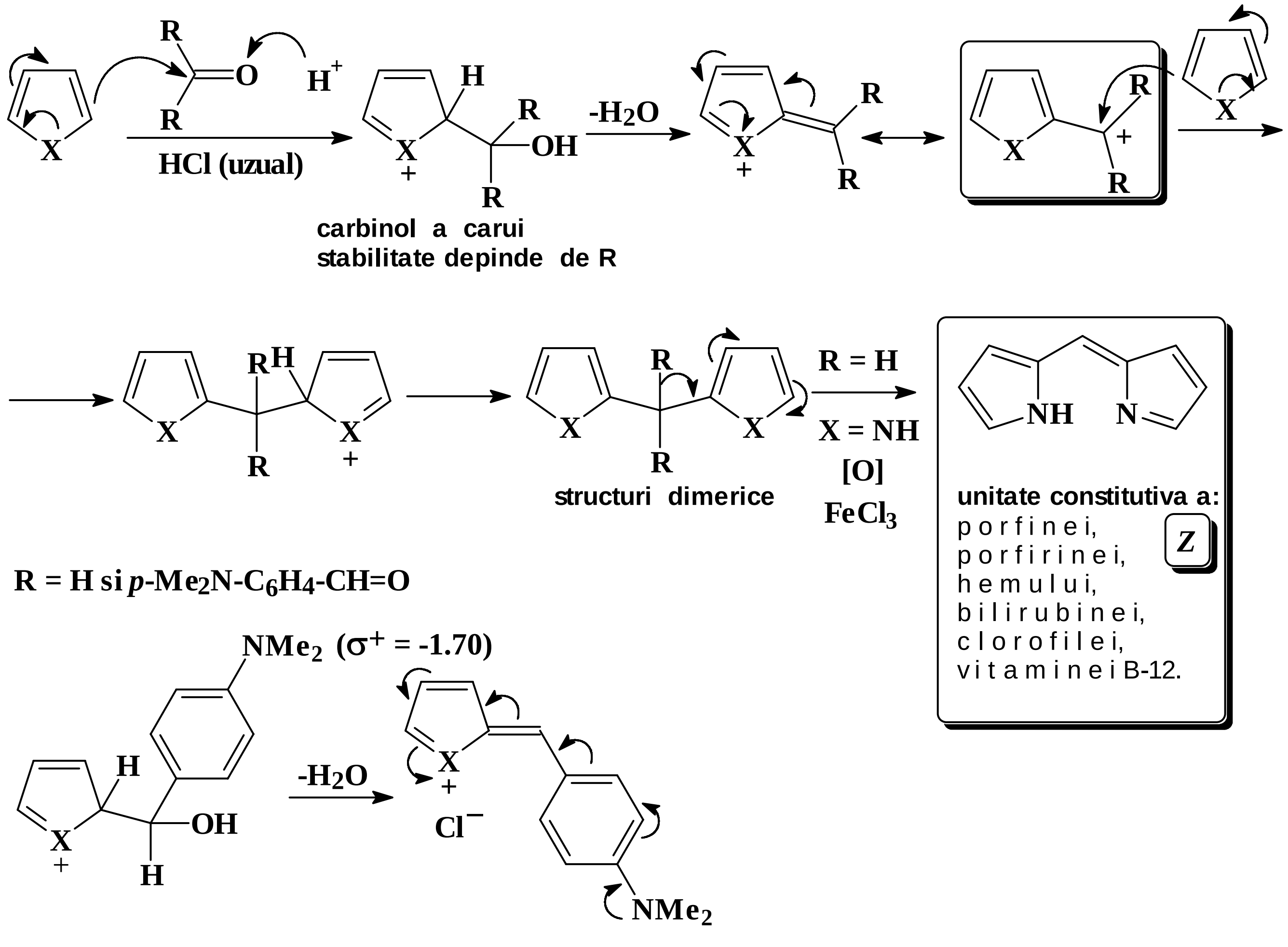


Ph-CO-Cl / $AlCl_3$ **Me-CO-Cl / $SnCl_4$** **EtBr / $AlCl_3$** **fara catalizator**

(X = O, NH neacetilabil)

Nota: pirolul si **furanul** sunt **instabili** fata de **acizii Lewis; complexarea (“otravirea”) $AlCl_3$** in **cazul tiofenului** se evita prin prepararea purtatorului de electrofil *a priori*. A se remarca similitudinea cu arenele, in cazul tiofenului.

e) (poli)condensarea cu electrofili de tip carbonil: aldehidic sau cetonic, in cataliza acida; specifica mai ales pirolului (si tiofenului).



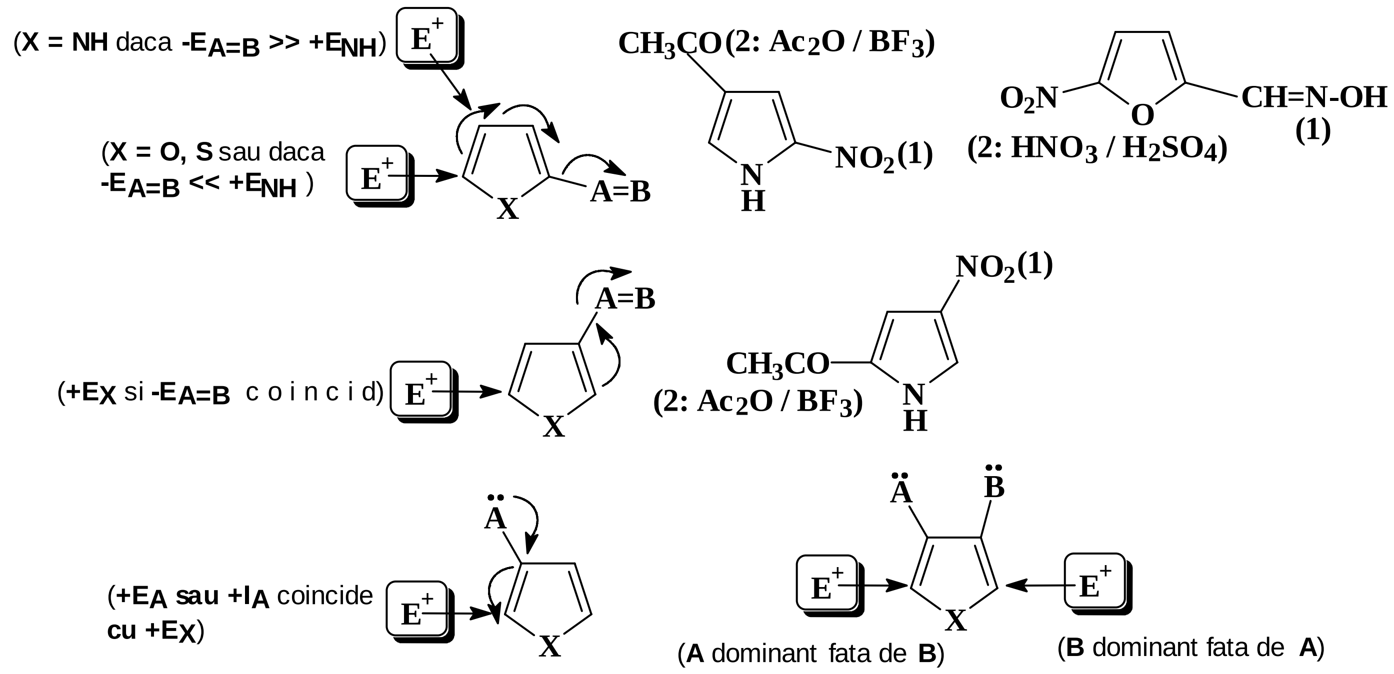
carbinol a carui stabilitate depinde de R

structuri dimerice

unitate constitutiva a:
porfinei,
porfirinei,
hemului,
bilirubinei,
clorofilei,
vitaminei B-12.

R = H si p-Me_2N-C_6H_4-CH=O

f) functionalizarea superioara prin substitutie electrofila:

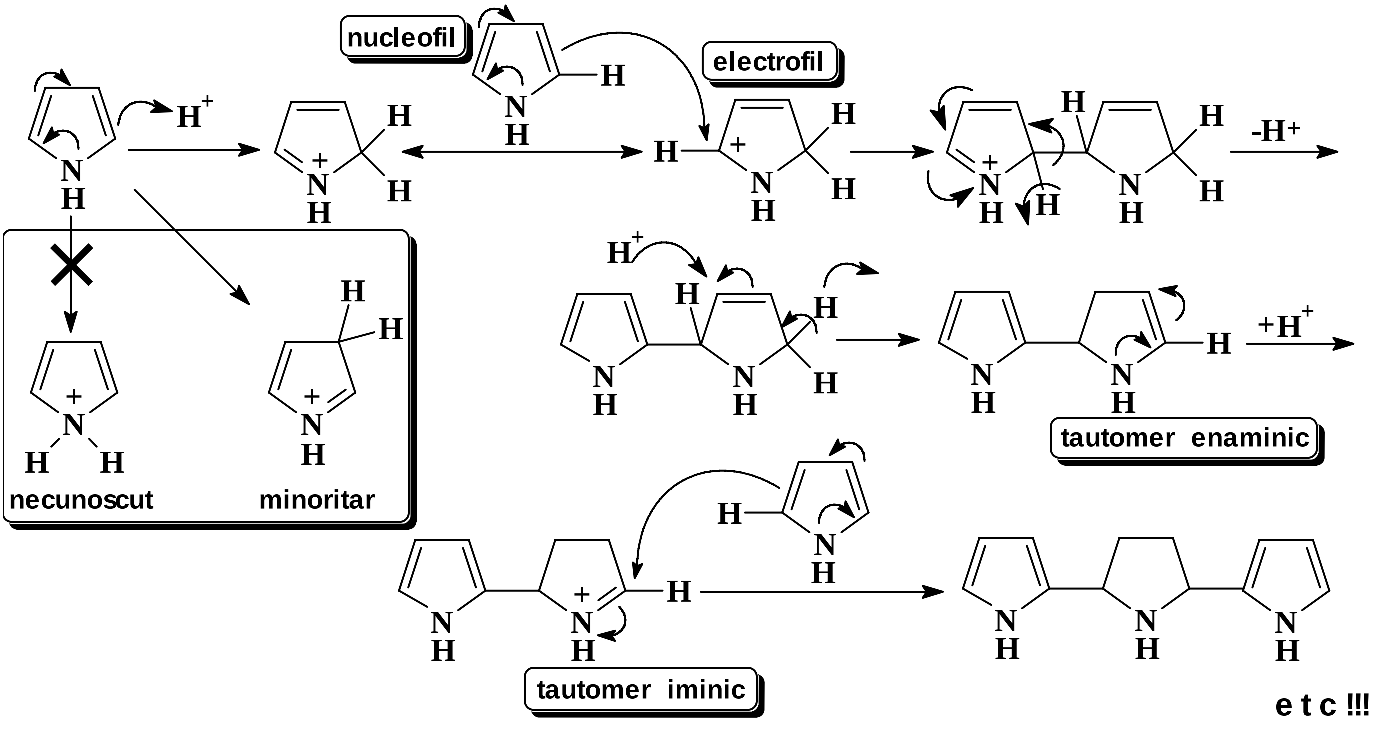


A=B, grupare cu efect **-E**; **A, B** = grupare cu efect **+E**, **+I**

Nota 1: functionalizarea superioara prin substitutie electrofila se practica atunci cand sintonii Knorr – Paal (sau Knorr) sunt inaccesibili
Nota 2: presubstituentii dezactivanti **(1)** maresc aromaticitatea hetarenei; **consecinta directa**: introducerea celui de-al doilea substituent **(2)** se realizeaza in conditii similare arenelor
Nota 3: pozitiile **C-2 SAU C-5** raman preferate (dar **diferentiate** ca reactivitate).

g) protonul ca electrofil:

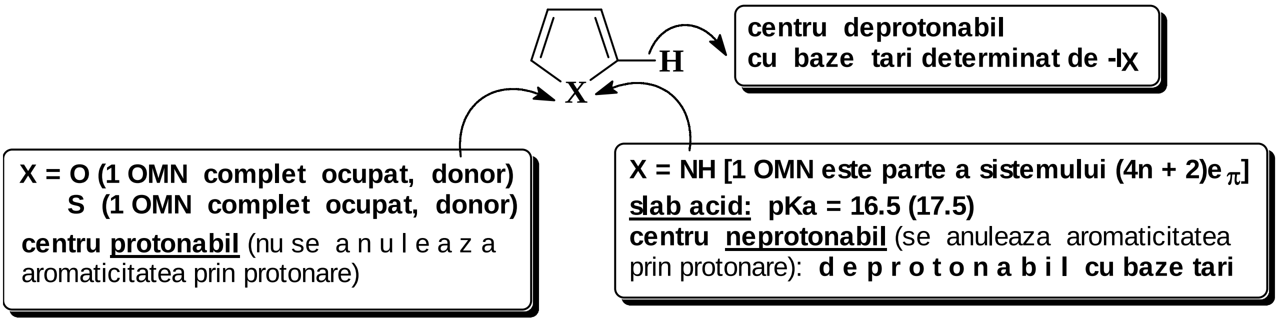
- **caracteristica generala** a reactivitatii **fata de acizii minerali tari, in exces, la t.a. sau la cald:** procese greu controlabile, neunitare: desfacere de ciclu si polimerizare, “rezinificare” (se pun in evidenta trasaturile de sistem 1,4-butadienic ciclizat cu un heteroatom).
- **furanul:** hidroliza, rezinificare; **tiofenul:** sulfonare, rezinificare; **pirolul**: polimerizare



3.1.2. Functionalizarea prin metalare

Generaliati:

- metalul este introdus substitutiv printr-un **echilibru acid – baza:**
    - la **heteroatom** (aspectul este relevant numai in cazul **pirolului**)
    - la **–CH=** heterociclic de la **C-2, -5**
- **rolul** metalului este acela de **a crea si/sau amplifica** (pe cat posibil **regioselectiv**):
    - **nucleofilicitatea** la **aza-atom** si / sau la **–CH=** heterociclic (**piroli**)
    - **nucleofilicitatea** la **–CH=** heterociclic (**tiofeni si furani**)

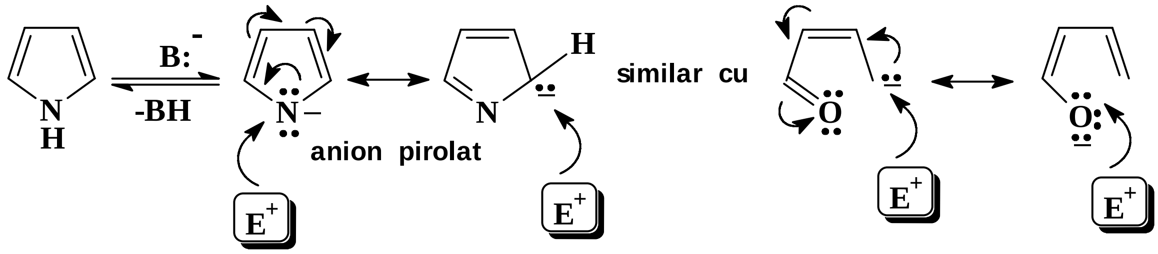


centru deprotonabil cu baze tari determinat de -I$_X$

X = O (1 OMN complet ocupat, donor)
S (1 OMN complet ocupat, donor)
centru protonabil (nu se anuleaza aromaticitatea prin protonare)

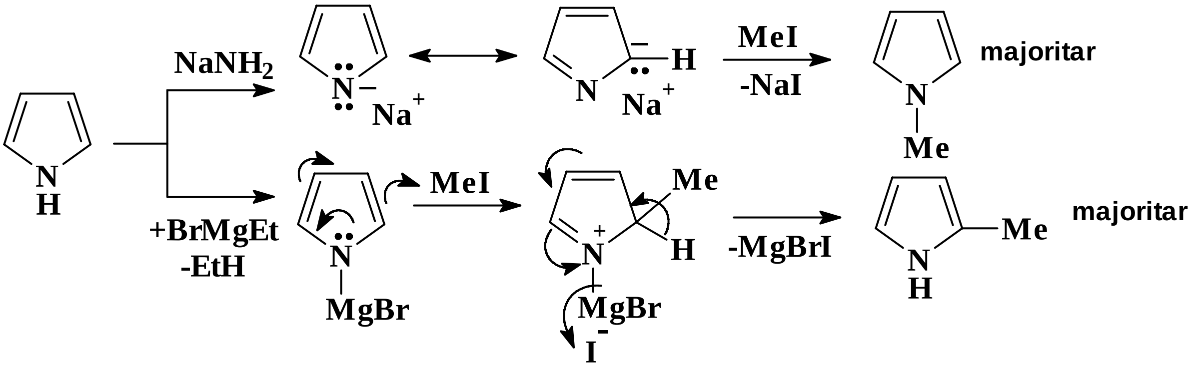
X = NH [1 OMN este parte a sistemului (4n + 2)e$_\pi$]
slab acid: pKa = 16.5 (17.5)
centru neprotonabil (se anuleaza aromaticitatea prin protonare): **deprotonabil cu baze tari**

a) functionalizarea prin metalare a pirolului:



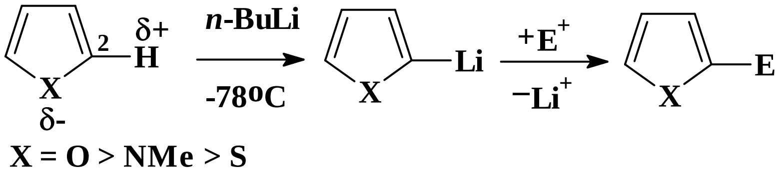
Nota 1: regioselectivitatea atacului electrofil depinde de **electropozitivitatea metalului** (relatia acestuia cu azotul heterociclic: ionica sau covalent polara).

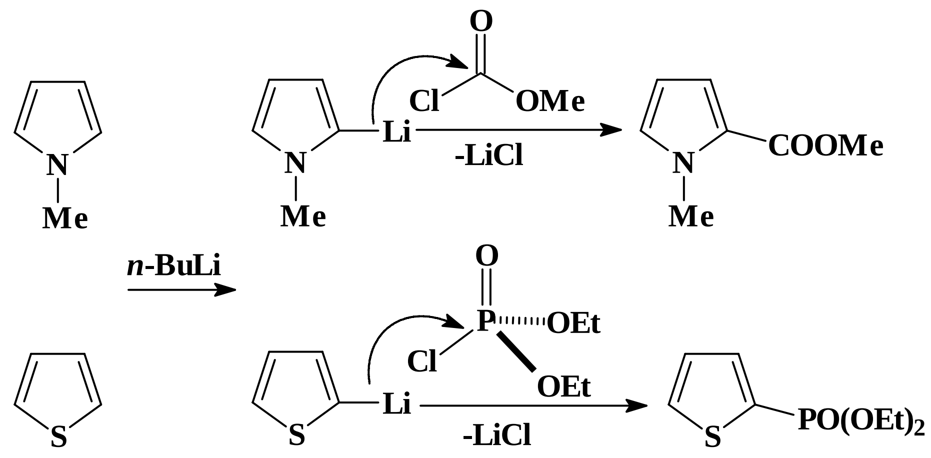
Nota 2: randamentul depinde de capacitatea bazei (**B:$^-$**) de a deplasa echilibrul acido – bazic in sensul deprotonarii (baze tari: **BrMgMe, NaNH$_2$, EtONa**).

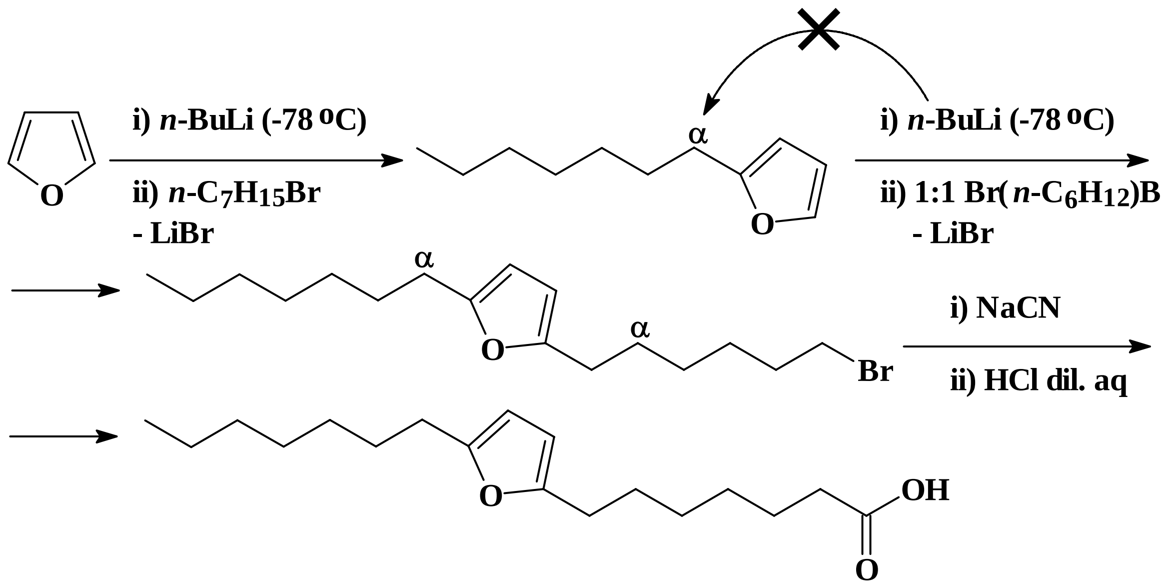


Nota 3: este posibila si derivatizarea ca structura N-acilata

b) functionalizarea prin litiere: regioselectiva la **C-2** (furan > N-metilpirol > tiofen); uzual *n*-BuLi la –78^{o}C.





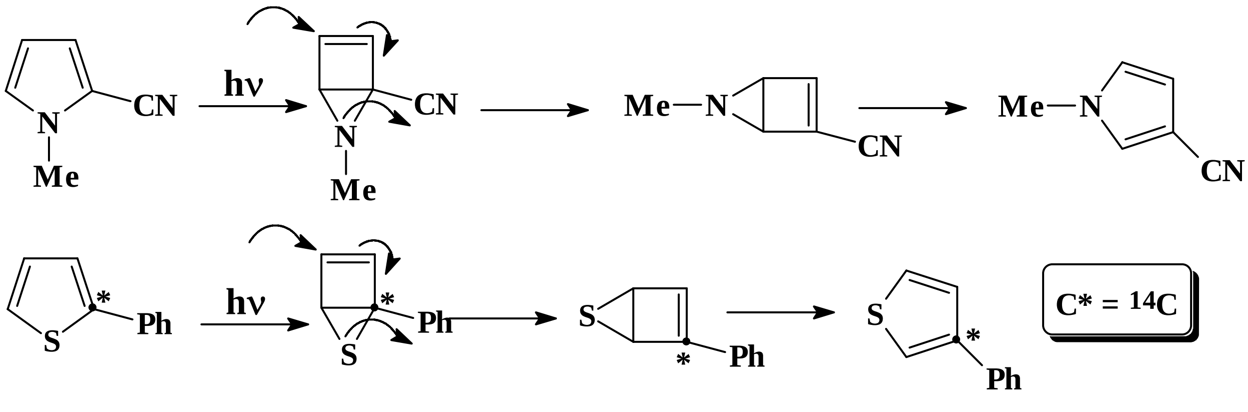


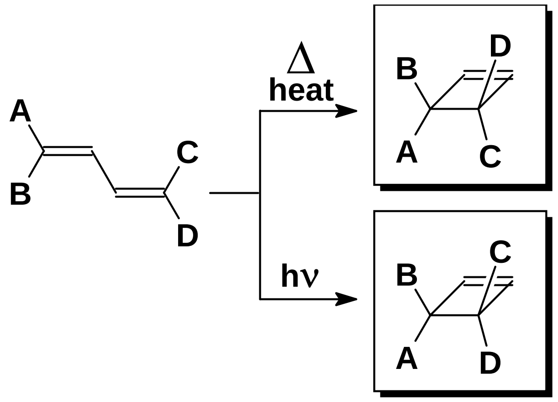
Nota: α-metilenii de la C-2 **nu sunt** deprotonabili cu *n*-BuLi

3.1.3. Transpozitii fotochimice

Consta din migrarea **aparenta** unui substituent de la **C-2** la **C-3**; este caracteristica generala a pentahetarenelor cu 1 – 3 heteroatomi; este o **rearanjare de schelet** si **nu o migrare efectiva** a substituentului

-nu are valoare preparativa.



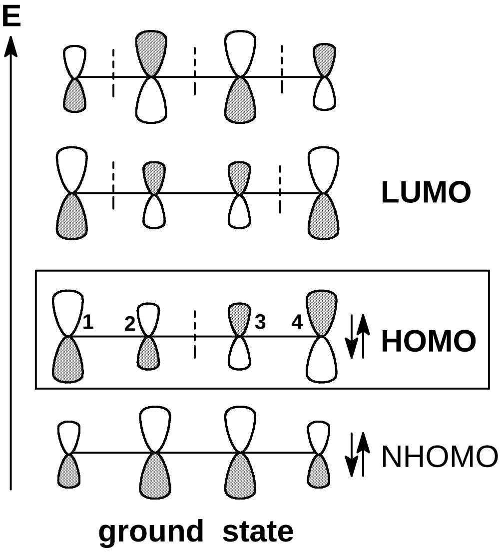


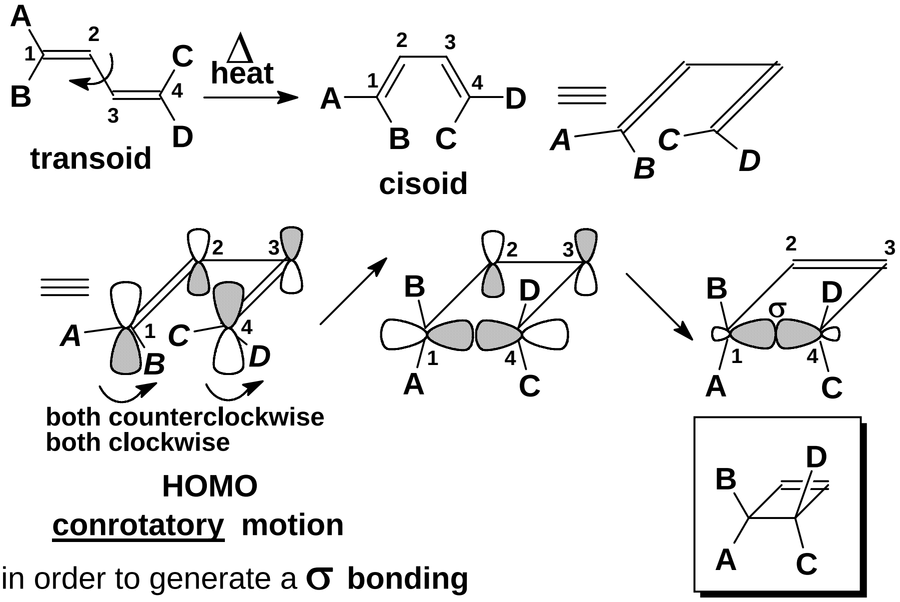
i) electrocyclic process
ii) 4n π-electrons are involved (*e.g.* n = 1)
ii) the stereochemistry of the ring closure is crucially influenced by the conditions

- THERMAL: Δ
- PHOTOCHEMICAL: hν

THERMAL CYCLISATION

LUMO: Lowest **U**noccupied **M**olecular **O**rbital
HOMO: Highest **O**ccupied **M**olecular **O**rbital
NHOMO: Next to **H**ighest **O**ccupied **M**olecular **O**rbital

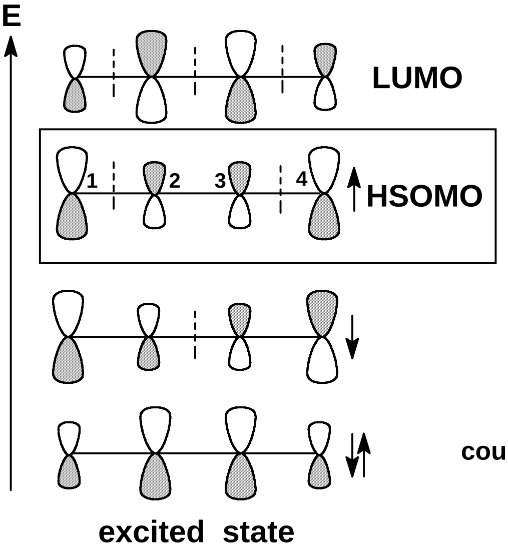


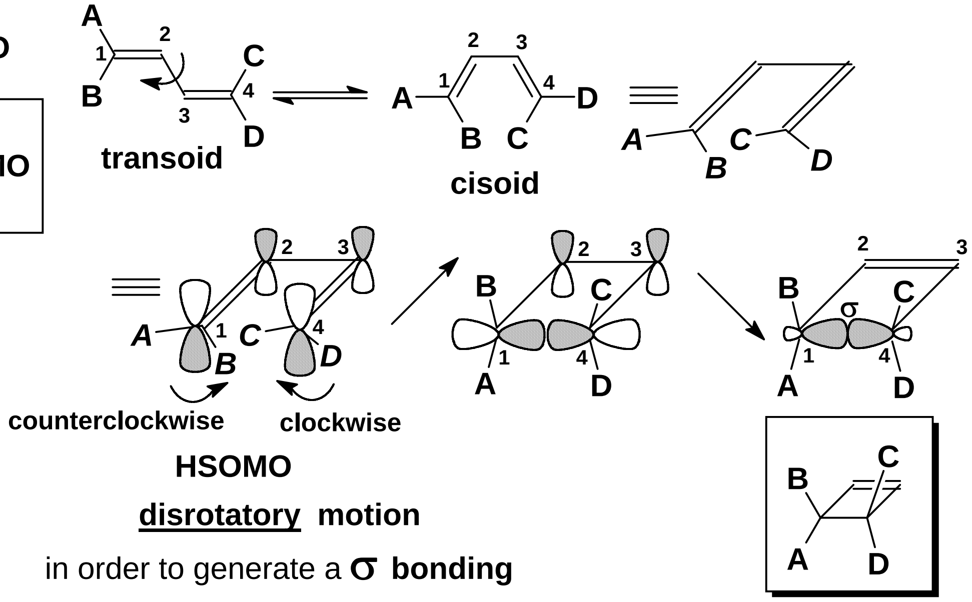


HOMO
conrotatory motion
in order to generate a σ **bonding**

PHOTOCHEMICAL CYCLISATION

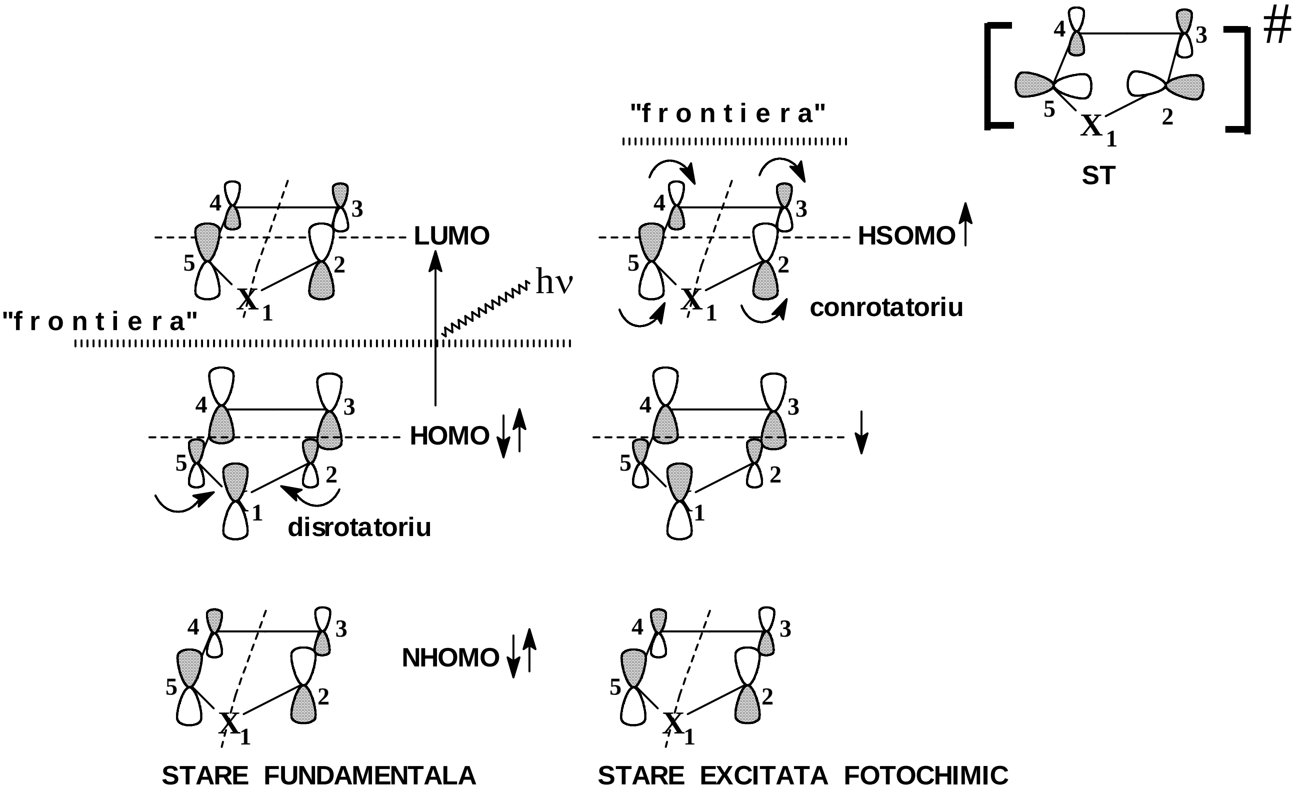
HSOMO: **H**ighest **S**ingle **O**ccupied **M**olecular **O**rbital





HSOMO
disrotatory motion
in order to generate a σ **bonding**

Regioselectivitatea ciclizarii:



- sistem heteroaromatic **(4n+2)e**$_{\pi}$
- sunt considerati numai orbitalii moleculari de frontiera **(OMF): HOMO** si **LUMO**
- prin iradiere, **HOMO (stare fundamentala) → HSOMO (stare excitata)**
- in **starea fundamentala**, interactia perturbationala favorabila:
  C-2 + C-5 inchidere disrotatorie permisa <u>termic</u> (in HOMO) neimportanta

- in **starea excitata fotochimic**, interactia perturbationala favorabila:
  C-2 + C-5 inchidere conrotatorie permisa <u>fotochimic</u> (in HSOMO) importanta