PYRIDINES

1. General

a) Typical representatives
b) Aromatic character
c) The base character

2. Syntheses

2.1. *Hantzsch* methodology
2.2. Industrial methods

3. Functionalisation

3.1. Functionalisation at (*via*) pyridine nitrogen
3.1.1. Coordination of Lewis acids and applications
a) Preparation of mild sulfonating reagents
b) Preparation of nitrating reagents for high substrate selectivity
c) Coordination complexes in redox and related processes
d) *N*-Acylium derivatives as *O*- and *N*-acylation reagents
e) *N*-Oxidation and pyridine *N*-oxides
f) *N*-Alkylation and its synthetic utility

3.2. Functionalisation by nucleophilic substitution
3.2.1. Nucleophilic substitution of hydrogen
a) Amination according to *Chichibabin*
b) Related reactions

3.2.2. Nucleophilic substitution of leaving groups
a) Nucleophilic substitution of halogen
b) Nucleophilic substitution of diazo groups and its synthetic utility

3.3. Functionalisation by electrophilic substitution
3.3.1. Electrophilic substitution of hydrogen in pyridine
a) Sulfonation
b) Nitration
c) Halogenation

3.3.2. Electrophilic substitution of hydrogen in some substituted pyridines
a) Nitration
b) Orientations of general interest

3.3.3. 2- and 4-Pyridones approach in electrophilic substitution in pyridine series

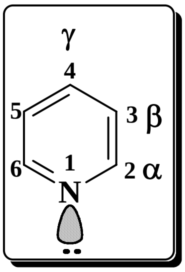
3.4. Functionalisation *via* metallation

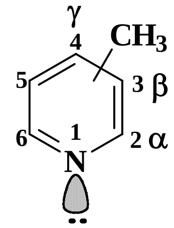
Modifications (improvements, additions, corrections, up to dates *etc.*) are subjected to no notice.

P I R I D I N E

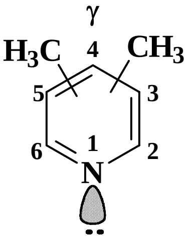
1. Generalitati:

a) reprezentanti tipici:





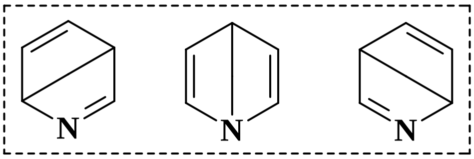
α,β,γ metilpiridine
PICOLINE



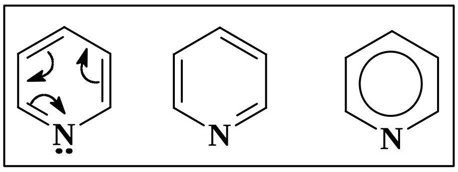
2,4-Dimetil-, 2,6-dimetilpiridine
LUTIDINE

b) caracterul aromatic:

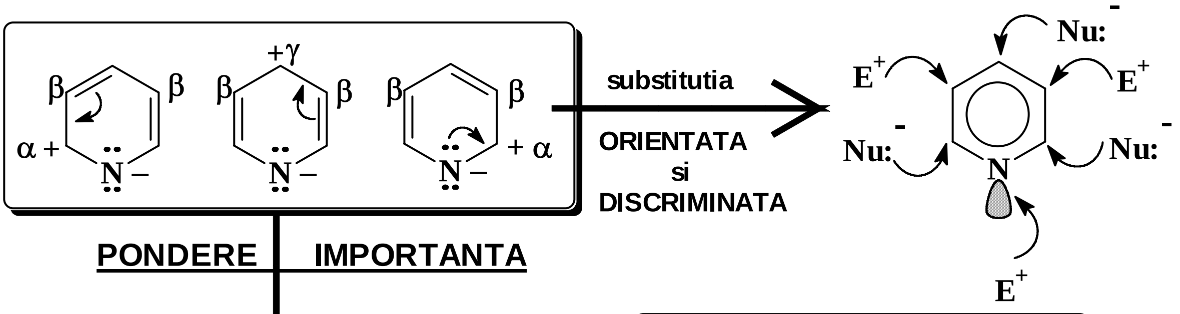
- **energia de conjugare:** similara benzenului, 36kcal / mol
- **prin inlocuirea une grupe** –CH= din benzen cu un ***azaatom*** **–N=** apar urmatoarele **trasaturi specifice:**



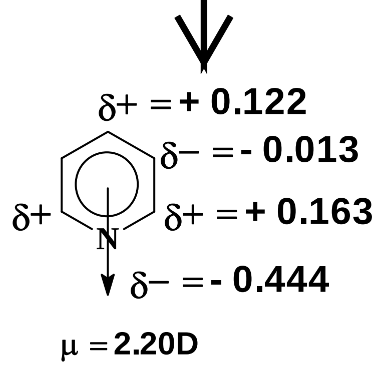
pondere **n e i n s e m n a t a**



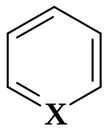
piridina "Kekulé" ⟶ **rezistenta la oxidare**
⟶ **rezistenta la hidrogenare**



PONDERE IMPORTANTA



S I S T E M E
(4n+2) π **D E F I C I T A R E**

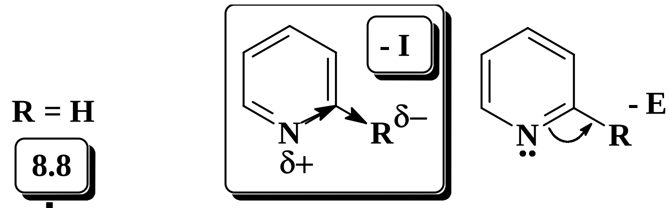


$X = N$: piridine
$X = O^+$: saruri de piriliu
$X = S^+$: saruri de tiopiriliu

c) caracterul bazic:

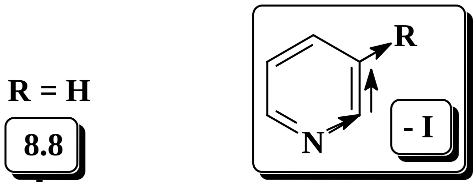
pKb a piridinei : 8.8

- consecinta a **electronegativitatii azotului**
- **caracterul aromatic** se realizeaza **fara contributia perechii neparticipante de la *N***
- **perechea neparticipanta** populeaza un **orbital de nelegatura** $\underline{sp^2}$ → **BAZA SLABA**



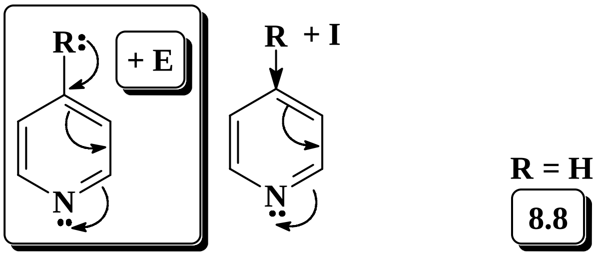
NH_2	CH_3	^{t}Bu	$CH_2=CH$	Ph	NHAc	*$CH(OH)_2$*	SMe	OMe	Cl	CN	NO_2
7.1	8.0	8.2	9.2	9.5	9.9	*10.2*	10.4	10.7	13.3	14.3	16.6

Bazicitate in scadere determinata de efectele -I (si -E)



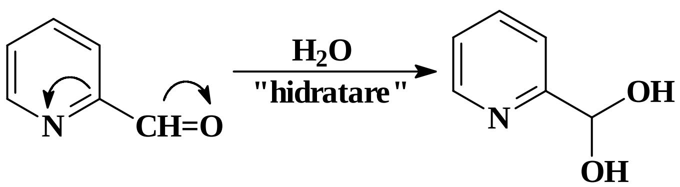
NH_2	^{t}Bu	CH_3	OMe	$CH_2=CH$	Ph	SMe	NHAc	*$CH(OH)_2$*	Cl	CN	NO_2
7.9	8.1	8.3	9.1	9.2	9.2	9.5	9.5	*10.2*	11.2	12.6	13.2

Bazicitate in scadere determinata de efectele -I



NH_2	OMe	CH_3	^{t}Bu	SMe	NHAc	$CH_2=CH$	Ph	$CH(OH)_2$	Cl	CN	NO_2
4.8	7.4	8.0	8.0	8.0	8.1	8.5	8.5	9.3	10.2	12.1	12.4

Bazicitate in scadere determinata de scaderea efectului +E (+I)



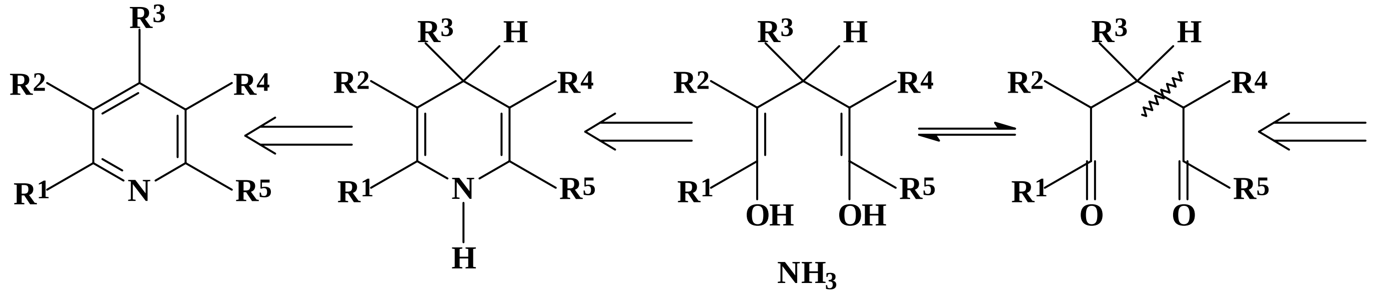
exemple conexe: CCl_3-CH=O stabil ca CCl_3-$CH(OH)_2$ etc.

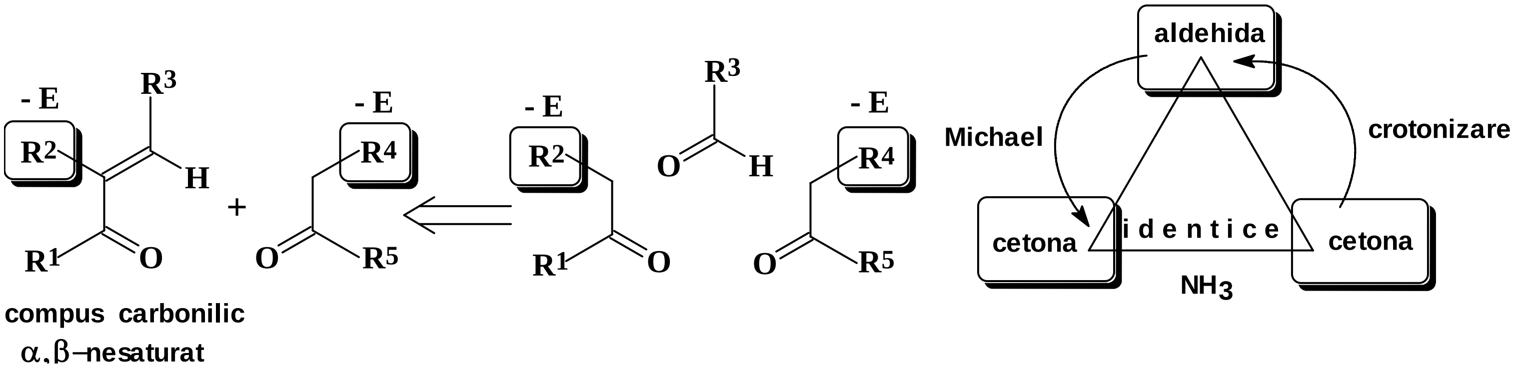
<u>Nota:</u> influenta substituentilor asupra bazicitatii se manifesta si prin **<u>rolul</u>** <u>lor</u> crucial in reactiile **SE, SN** la ***C*** sau ***N*.**

2. Sinteze:

- in general, sursa principala de piridine o formeaza **gudroanele carbunilor de pamant**
- prin sinteza, sunt accesibile **piridinele substituite**
- **varietatea de piridine** substituite este asigurata de **reactiile de functionalizare**

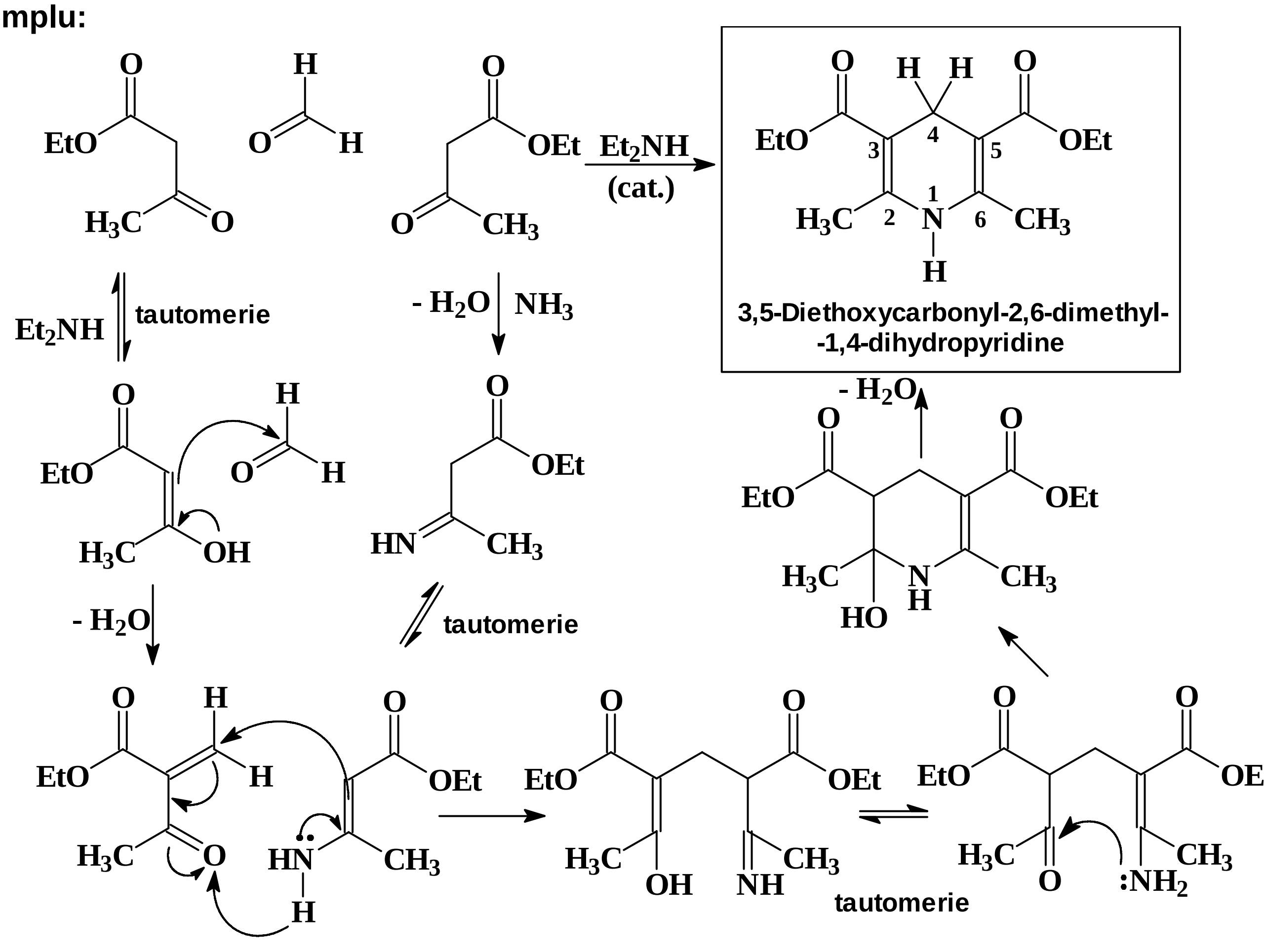
2.1. Metoda Hantzsch (1882)



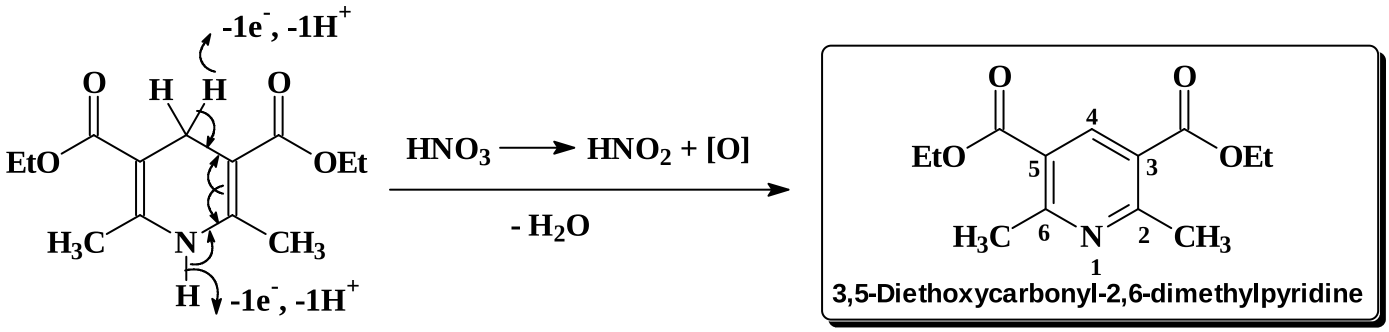


- este **metoda clasica : condensare + oxidare**
- de obicei, **cele doua cetone** sunt **identice (iar $R^1 \equiv R^5$ si $R^2 \equiv R^4$** de **tip ester)**

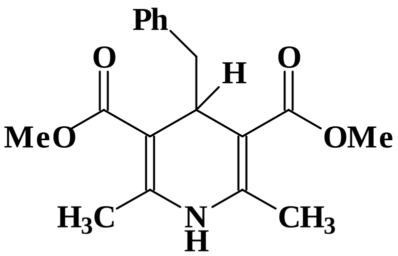
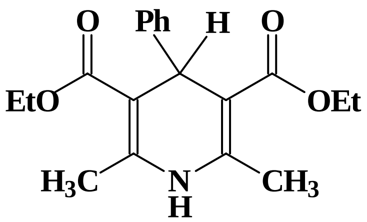
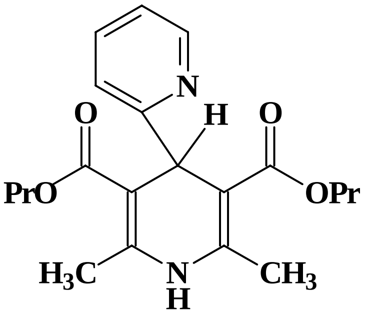
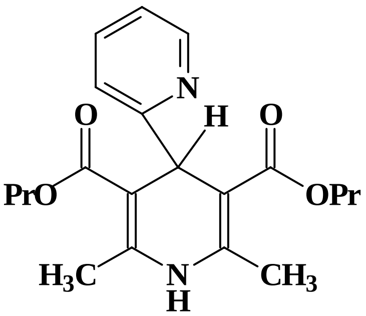
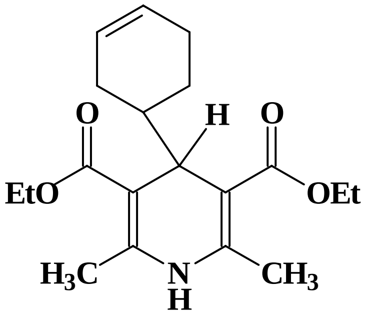
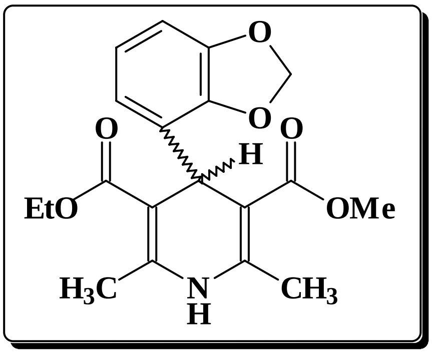
Exemplu:



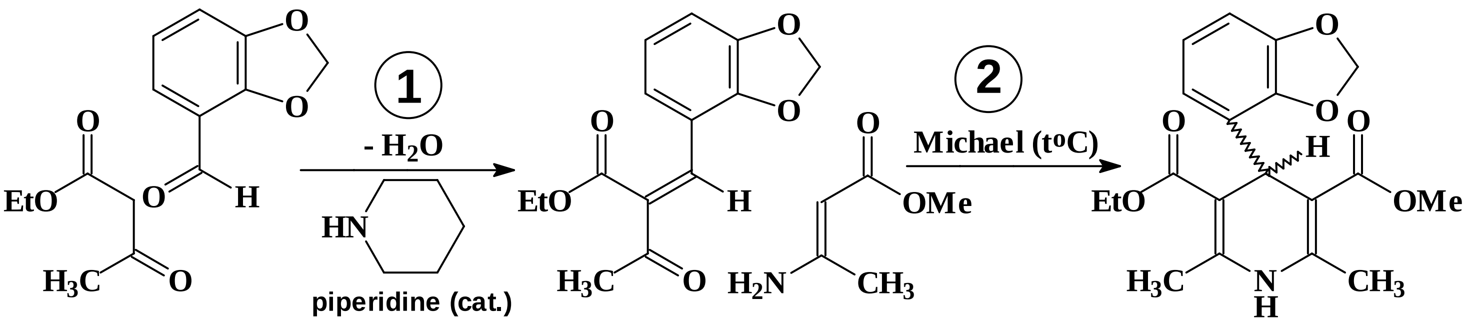
- **practic, nu conteaza succesiunea <u>exacta</u> a proceselor deoarece se incalzeste amestecul celor doua componente in proportie stoechiometrica.**
- 1,4-dihidropiridinele intermediare **pot fi izolate**
- **oxidarea** lor conduce la **piridinele corespunzatoare**



- alte **1,4-dihidropiridine importante**, obtinute pe **aceeasi cale (dupa SmithKline Beecham Pharmaceuticals®)**

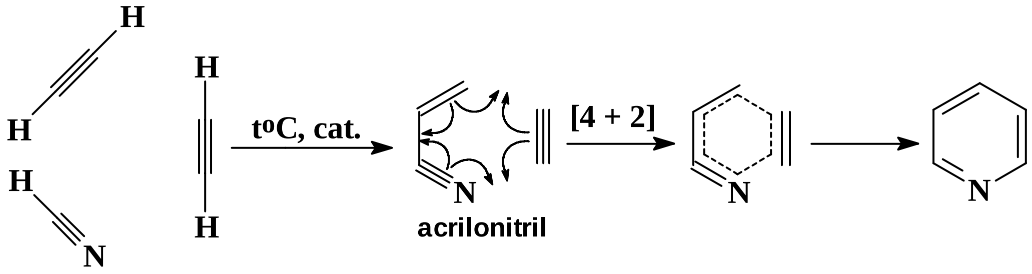







- in cazul prezentei de **substituenti diferiti la** ***C*** **- 2, - 6**, partenerii cetonici **(diferiti)** se introduc **succesiv**, de exemplu la prepararea **dihidropiridinelor chirale**.



2.2. Metode industriale:

- **piridina ca atare:**



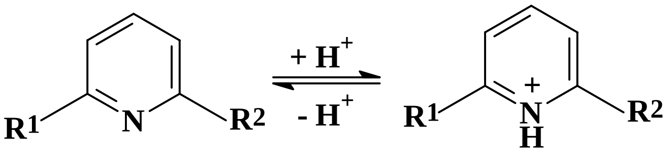
Nota: proces concertat de cicloaditie (1,4-dipolara)

3. Functionalizarea

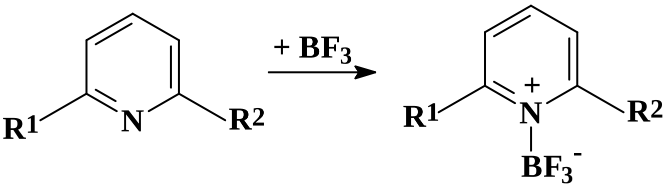
3.1. Functionalizarea la (*via*) *N* – piridinic

- **proces fundamental, influentat de:**
  - **a) bazicitatea atomului de azot piridinc**
  - **b) efectele sterice ale substituentilor de la *C* - 2, - 6**

Exemplu: influenta efectelor sterice



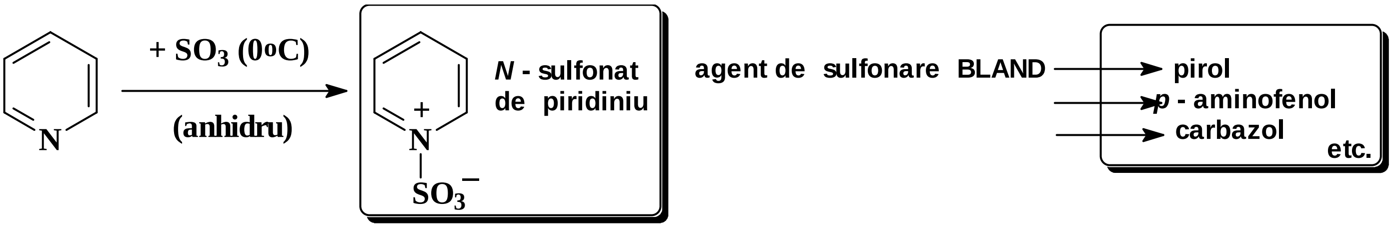
R^1	H	*t*Bu	*t*Bu	Me
R^2	H	H	*t*Bu	Me
pK_b	8.8	8.2	10.4	7.4



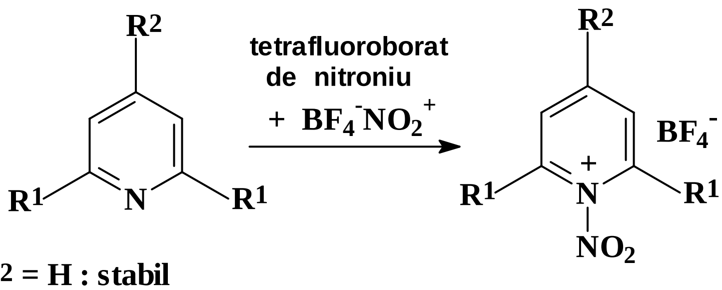
R^1	H	Me	Me
R^2	H	H	Me
Hf (kcal/mol)	- 32.9	- 31.2	- 25.4

3.1.1. Coordinarea acizilor Lewis si aplicatii:

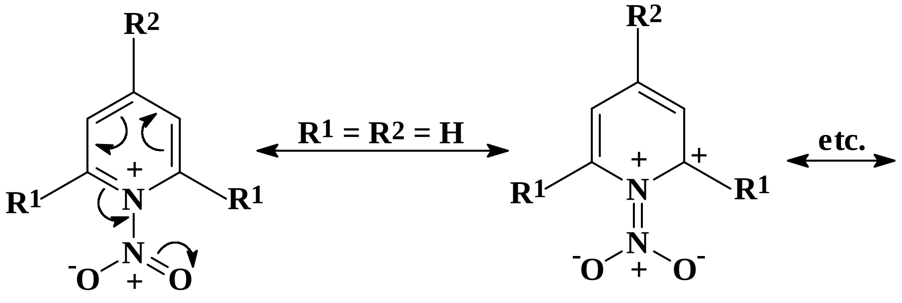
a) prepararea de agenti de sulfonare blanzi, pentru **sulfonari ireversibile:**

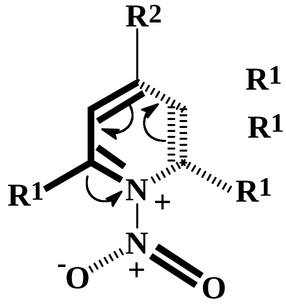


b) prepararea de agenti de nitrare cu mare selectivitate de substrat:



$R^1 = R^2 = H$: stabil
$R^1 = Me$; $R^2 = H$: instabil, agent de nitrare SELECTIVA in seria arenelor
$R^1 = Me$; $R^2 = OMe$: instabil, agent de nitrare SELECTIVA in seria arenelor
(*e.g.* $k_T / k_B = 44.5$)



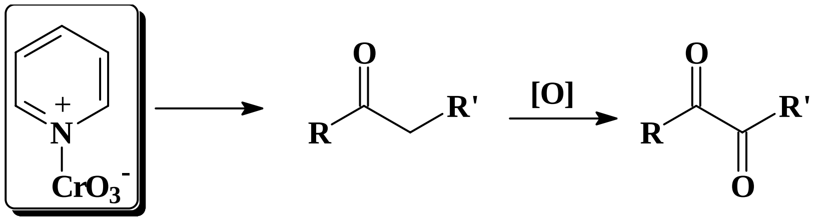


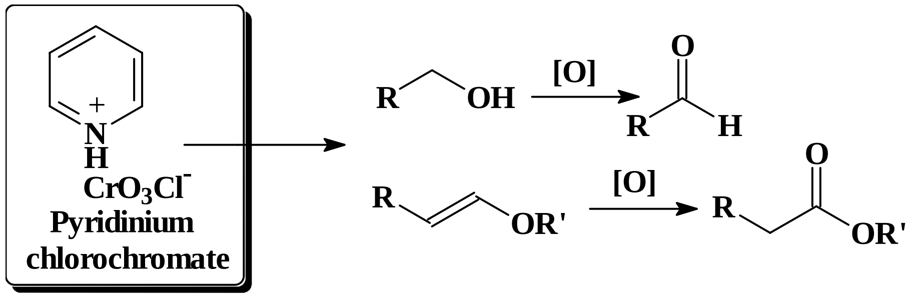
R^1 = Me; R^2 = H, deviere de la coplanaritate, legatura *N* - *N* <u>slaba</u>

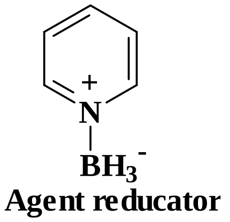
R^1 = Me; R^2 = OMe, deviere de la coplanaritate combinata cu <u>marirea bazicitatii</u> la *N* - piridinc (+ E $_{OMe}$!)

<u>c) complecsi de coordinare in procese redox si inrudite:</u>

- agenti de oxidare: selectiva

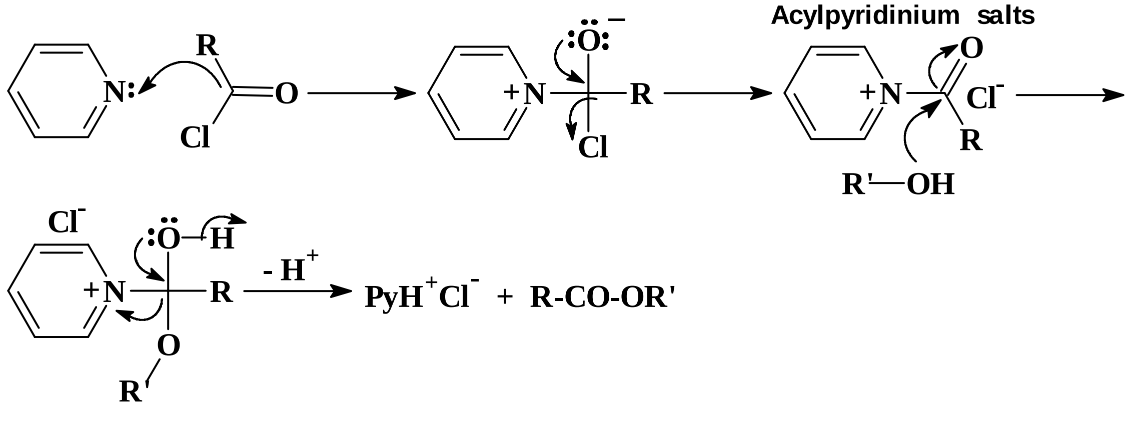




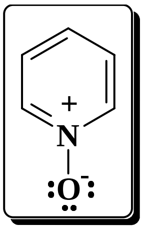


<u>d) derivati de *N* – acilpiridiniu ca agenti de *O*- (si *N* – acilare):</u>

- similari **imidazolidei**, furnizeaza **(echivalenti) electrofili** de **tipul RC$^+$=O din cloruri acide (R-CO-Cl) sau anhidride (R-CO)$_2$O:**



e) *N* – oxidarea; piridin *N* – oxizi:



proces de **importanta preparativa fundamentala** deoarece:

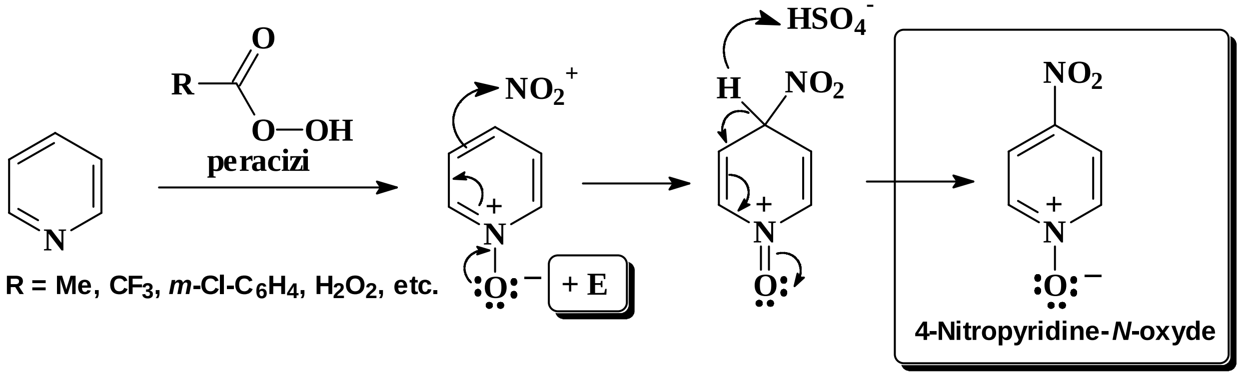
i) faciliteaza efectuarea de **reactii SE** pe inelul piridinic **(analog unor** procese **SE** ale **anionilor fenoxid)** foarte regioselectiv la *C* - 4
ii) permite efectuarea de reactii **SN** pe **inelul piridinic**
optiunea in directia SE sau SN depinde de reactant
iii) permite reducerea *N* – oxidului la structura **piridinca initiala**

Exemplul 1: nitrarea la *C* – 4

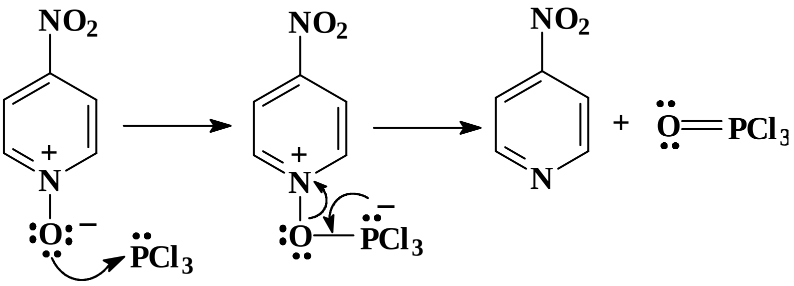
- **furnizeaza 4-nitroderivatul ca sursa de alti derivati fundamentali**

i) oxidarea si nitrarea (SE)

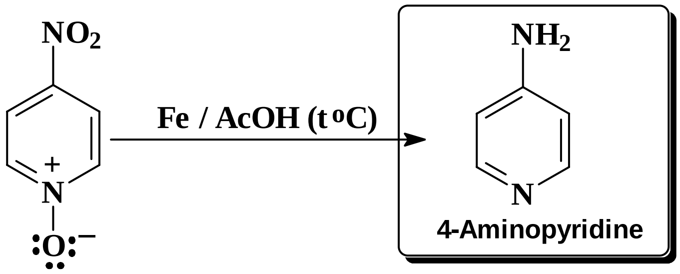
$$HNO_3 + 2H_2SO_4 \rightleftharpoons NO_2^+ + 2HSO_4^- + H_3O^+$$

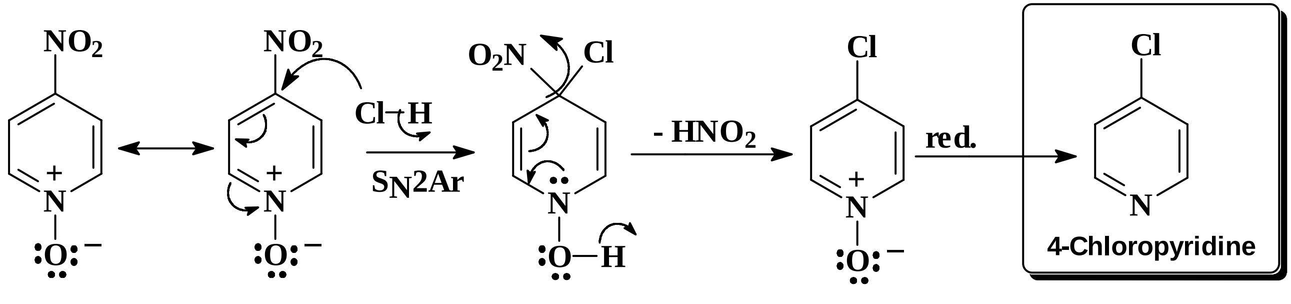


ii) reducerea: agent tipic PCl_3 sau Fe / AcOH:

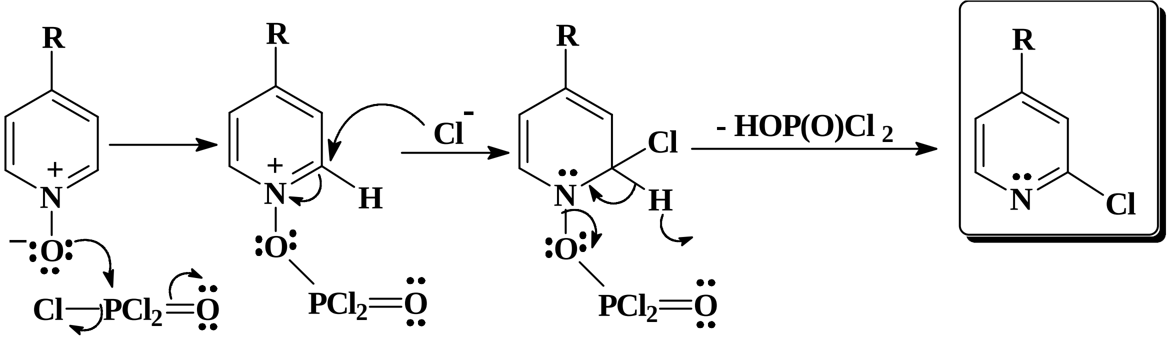


- **directii de valorificare ale 4-nitropiridin-*N*-oxidului:**



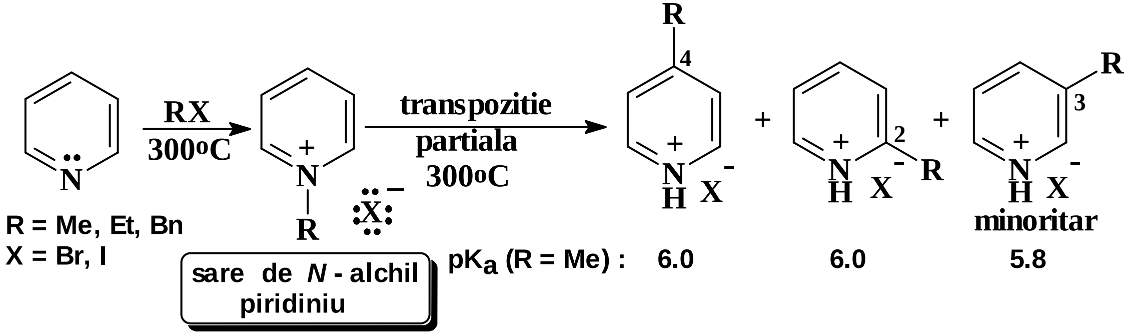


Exemplul 2: generalizarea metodei un cazul altor piridin ***N* – oxizi** la prepararea **2 – cloropiridinelor** → **concomitent** cu **halogenarea prin SN** are loc **si reducerea, sub actiunea $POCl_3$:**



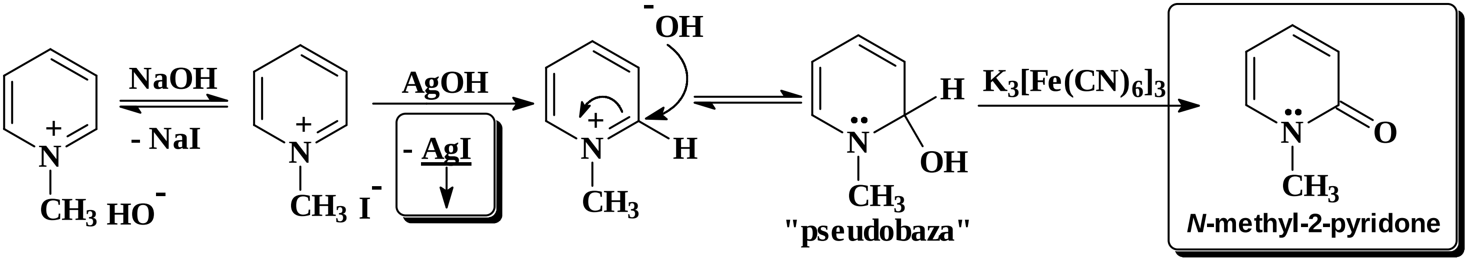
f) *N* – alchilarea si valoarea preparativa

- proces **SE** la ***N* – piridinic** (**S_N2** cu **piridina** ca **nucleofil**)
- **analog** obtinerii **sarurilor cuaternare de amoniu din amine tertiare**
- sursa de electrofili este si ea analoaga: **derivati halogenati cu reactivitate normala sau marita**, sulfati de alchil

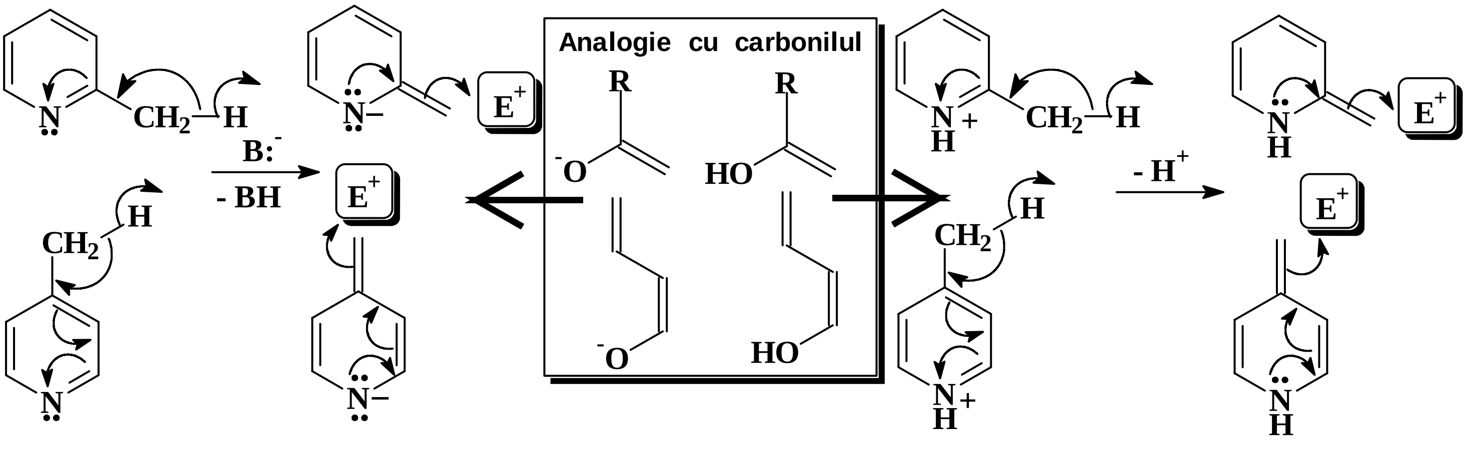


Nota: **migrarea grupei alchil** (**partiala !**) are loc astfel ca sa se formeze **alchilpiridinele** cele mai **bazice.**

- sarurile de ***N* - alchilpiridiniu** sunt **mult mai reactive** fata de **nucleofili** decat **piridina** ca atare



- **grupele metil** de la ***C* – 2 (- 6), - 4** (**nu** si de la ***C* – 3 !**) din **metilpiridine** sunt **metileni activi** (cat. acido – bazica) **si permit** **functionalizare avansata**

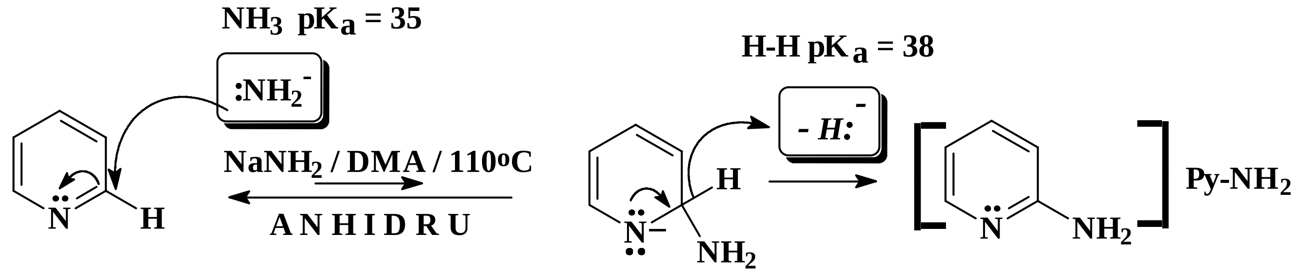


3.2. Functionalizarea prin substitutie nucleofila

3.2.1. Substitutia nucleofila a hidrogenului

a) Aminarea dupa *Chichibabin*

- metoda **clasica** de preparare a **2 - aminopiridinei:**



$$\underset{\text{acid}}{Py\text{-}NH_2} + \underset{\text{baza}}{Na^+H:^-} \longrightarrow Py\text{-}NH^-Na^+ + \boxed{H_2\,(g)} \longrightarrow$$ **asigura *ireversibilitatea***

$$\underset{\text{acid}}{Py\text{-}NH_2} + \underset{\text{baza}}{Na^+NH_2^-} \longrightarrow Py\text{-}NH^-Na^+ + NH_3\,(g)$$

$$\boxed{\text{Final:}}\ Py\text{-}NH^-\,Na^+ + \boxed{H_2O} \longrightarrow Py\text{-}NH_2 + NaOH$$

Nota 1: mecanismul ***propus*** este in acord cu aspectul experimental al degajarii celor **doua gaze.**

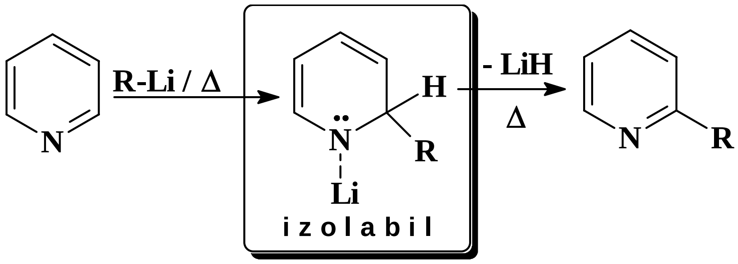
Nota 2: reactia are loc totdeauna la *C* – 2

Nota 3: 4-aminopiridina se formeaza (in varianta **Chichibabin**) doar ca **produs secundar**, alaturi de derivatul **2,6-diamino**; devine **produs majoritar** doar daca pozitiile ***C* - 2** si ***C* – 6** sunt ocupate cu grupe nefugace (alchil).

Nota 5: analogii alcalini **$R\text{-}NH^-Na^+$, $R_2N^-Na^+$ si $R\text{-}NH\text{-}N^-Na^+$** reactioneaza **similar.**

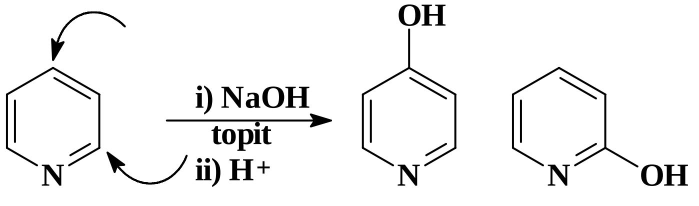
b) Reactii inrudite:

- alchilarea (arilarea) cu reactivi litioorganici: ***Ziegler* alkylation**



R = alchil (inferior) : alchilare
R = Ar : arilare

- **topirea alcalina:** metoda **nepredilecta**

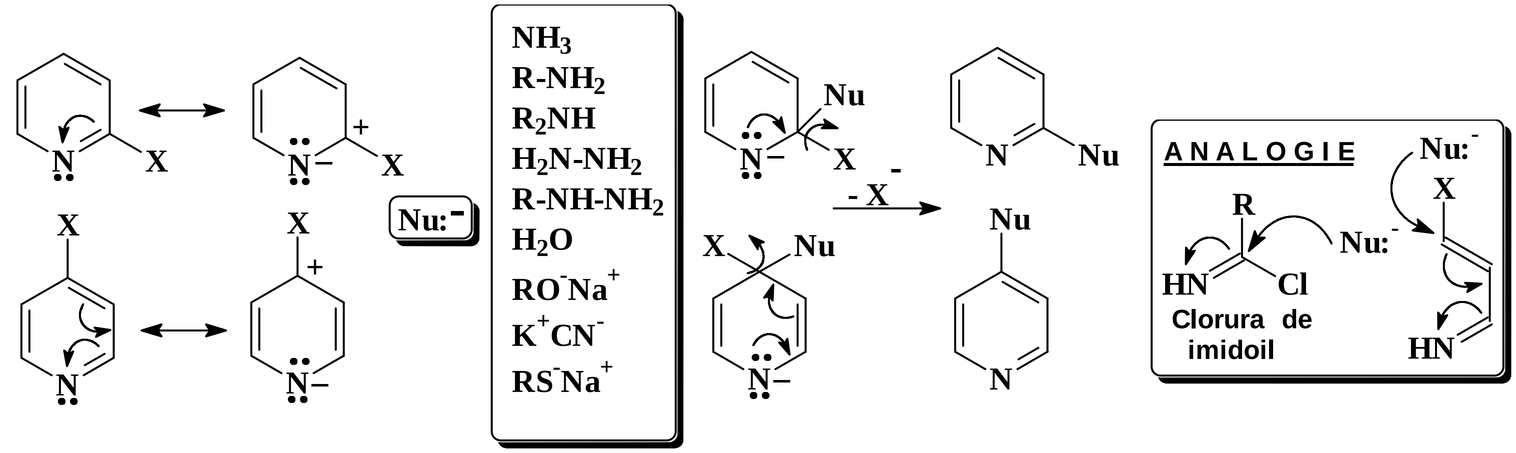


α (γ)– **hidroxipiridina**

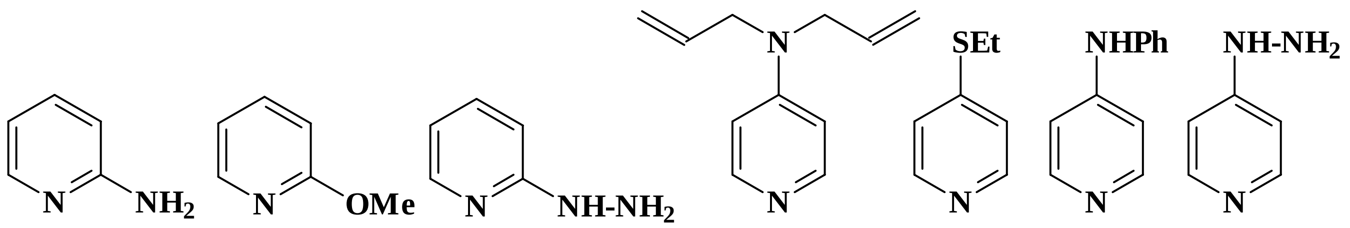
3.2.2. Substitutia nucleofila a grupelor fugace:

a) Substitutia nucleofila a halogenului:

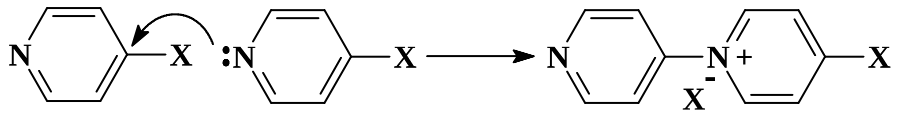
- are loc <u>cu usurinta</u> in cazul **2 (α) – sau 4 (γ) – halopiridinelor**, similar **analogilor halonitrobenzeni**
- **3 (β)** – halopiridinele sunt **autentici compusi halogenati** cu **<u>reactivitate scazuta</u>**
- capacitatea **halogenului** ca **LG scade** odata cu **electronegativitatea: $F^- > Cl^- > Br^- > I^-$**
- **prezenta** suplimentara de **grupe cu efect –E (NO_2) mareste** considerabil **reactivitatea.**



Nota: sunt procese analoage unor S_N2Ar (Jackson – Meisenheimer), la **incalzire (moderata)**
Exemple:

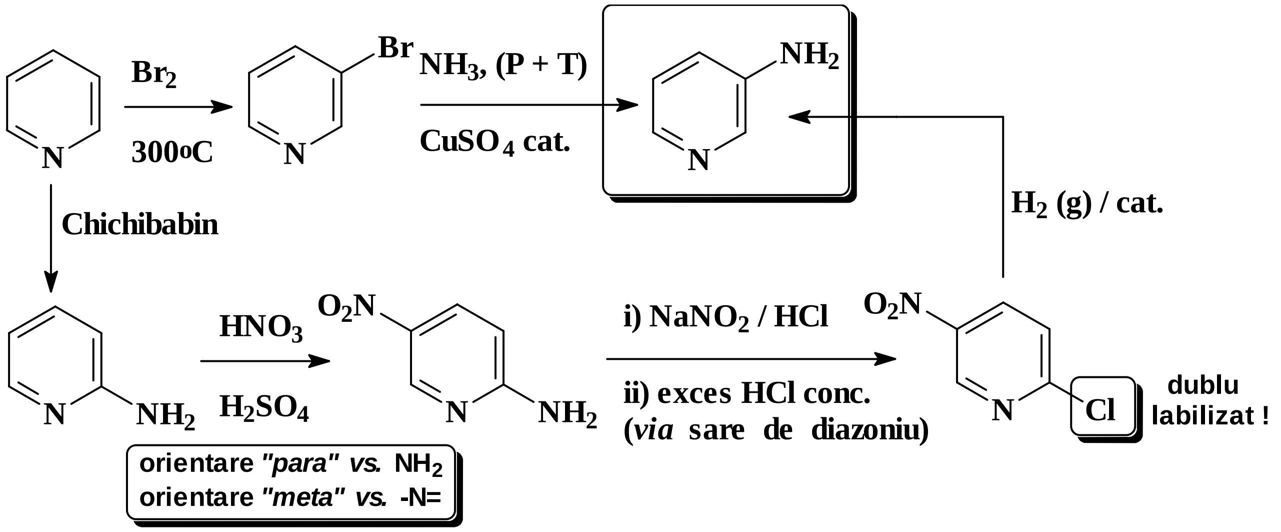


- in general, **4 – halopiridinele** sunt **mai reactive ca 2 - halopiridinele:**



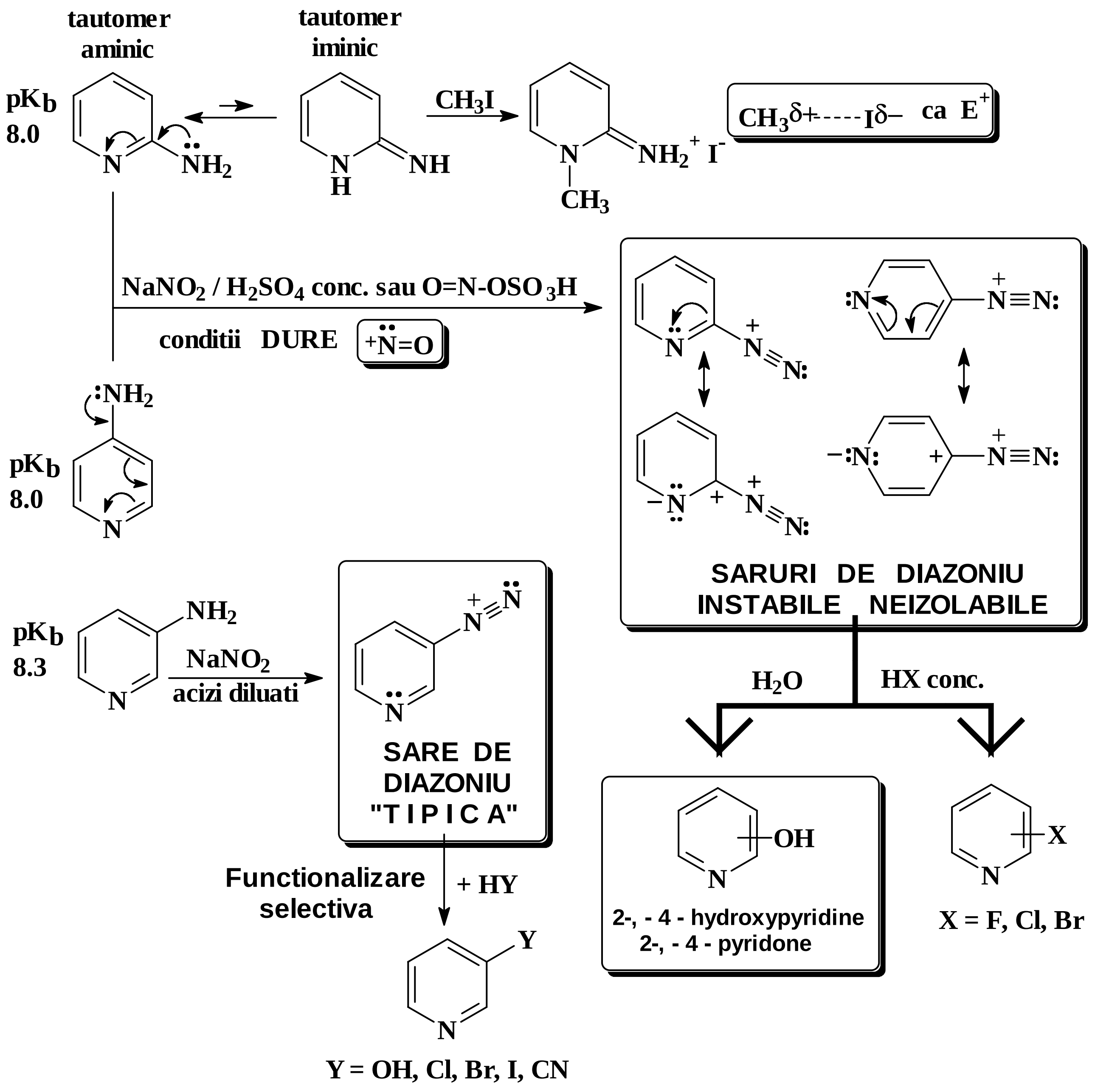
X = Cl: la t.a.
X = Br: proces lent, la 0°C
X = F : reactie spontana

- pentru obtinerea **3 – aminopiridinei**, se aplica **metode indirecte ("m u l t i s t e p"):**



b) Substitutia nucleofila a grupelor diazoniu si importanta preparativa

- **permite inlocuirea grupei diazo de la *C* – 2, - 4 cu grupa hidroxil si accesul la piridone, ca substraturi apte pentru functionalizarea prin substitutie electrofila**



Nota 1: diazoniul, ca **LG** urmeaza un mecanism **S_N1Ar**.

$$\mathrm{Ar}\text{-}\overset{15(14)}{\overset{+}{N}}\equiv\overset{14(15)}{N} \rightleftharpoons [\mathrm{Ar}^{+}\ N_2] \rightleftharpoons \mathrm{Ar}^{+} + \overset{14\ 15}{N_2}\quad \text{lent}$$

$$\mathrm{Ar}^{+} + \mathrm{Nu:}^{-} \rightleftharpoons \mathrm{Ar\text{-}Nu}\quad \text{rapid}$$

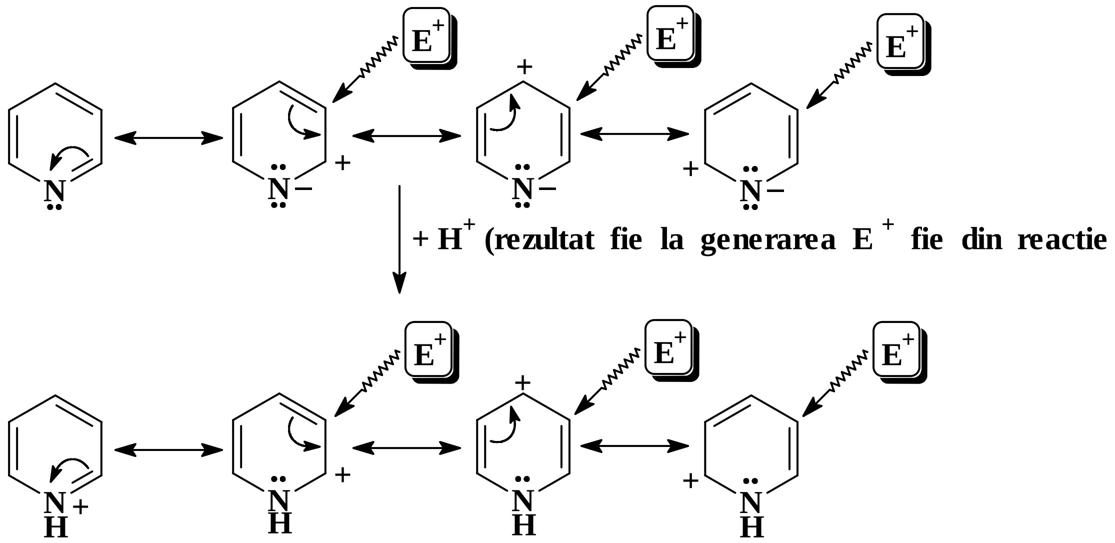
Nota 2: numai 3 – aminopiridina se comporta **similar** unei **amine aromatice tipice**

Nota 3: valorile **pK_b** ale **aminopiridinelor** (ca **substrat diazotabil) se refera** la ***N* – piridinc** si reflecta **influenta** acestuia asupra **grupei aminice, diazotabila** (vazuta ca **nucleofil** fata de ionul de **nitrozoniu).**

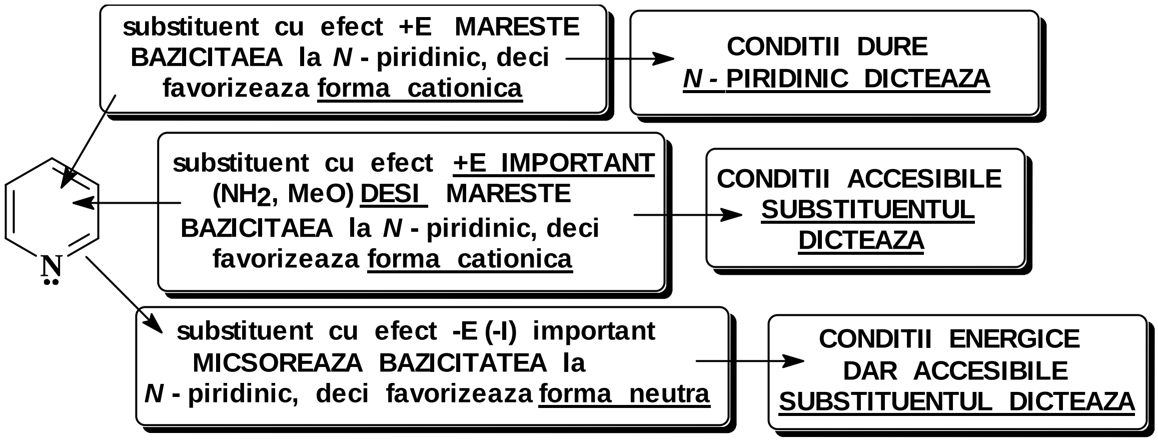
3.3. Functionalizarea prin substitutie electrofila

Generalitati:

- **proces defavorizat** de catre ***N* – piridinc** (**dezactivant**, analog unei **grupe cu efect puternic –E**)
- **proces inca mai defavorizat** de catre ***N* – piridinic protonat** (cationii piridiniu) cand **electrofilul** este concurat de catre **proton**
- **conditiile de reactile sunt dure si subatitutia are loc, de regula, in pozitia 3 (γ)**
- **sunt procese SE, in general, IREVERSIBILE**



- **aprecierea aproximativa a efectelor electronice ale substituentilor:**



substituent cu efect +E MARESTE BAZICITAEA la *N* - piridinic, deci favorizeaza forma cationica

CONDITII DURE *N* - PIRIDINIC DICTEAZA

substituent cu efect +E IMPORTANT (NH_2, MeO) DESI MARESTE BAZICITAEA la *N* - piridinic, deci favorizeaza forma cationica

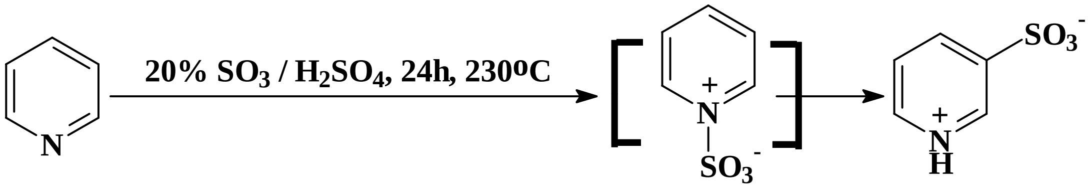
CONDITII ACCESIBILE SUBSTITUENTUL DICTEAZA

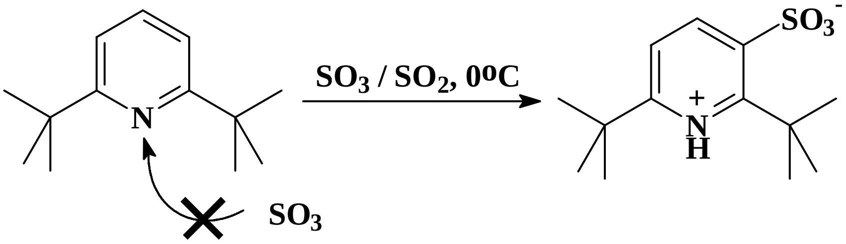
substituent cu efect -E (-I) important MICSOREAZA BAZICITATEA la *N* - piridinic, deci favorizeaza forma neutra

CONDITII ENERGICE DAR ACCESIBILE SUBSTITUENTUL DICTEAZA

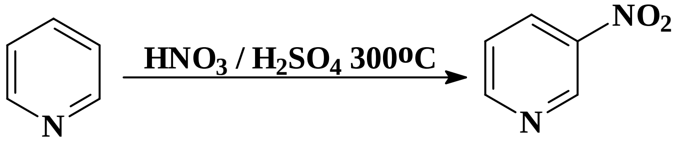
3.3.1. Substitutia electrofila a hidrogenului in piridina ca atare

a) Sulfonarea:





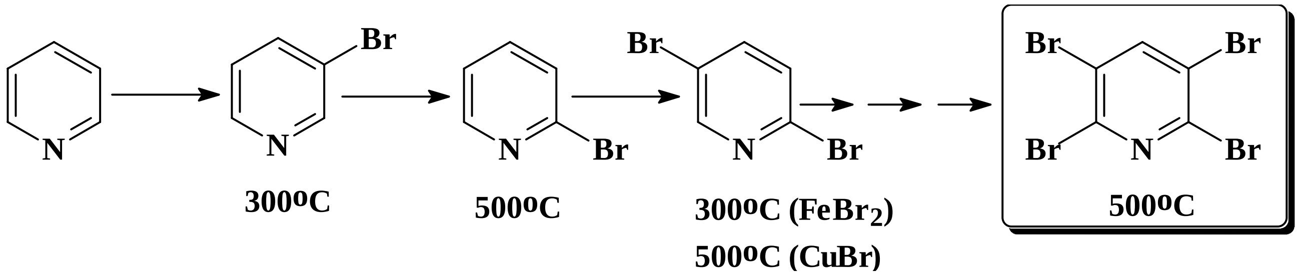
b) Nitrarea:



Nota: randamentul este de doar **cateva procente**

c) Halogenarea:

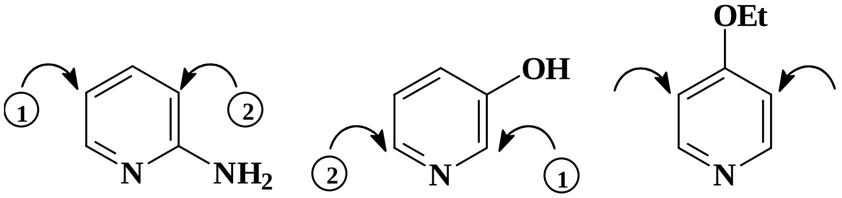
- **halogenarea directa** prezinta interes **numai in faza de vapori**, **catalitic**, conditii in care **formele protonate** ale substraturilor **nu sunt stabile** si **reactia are loc asupra speciilor neutre**
- **bromurarea este cea mai bine investigata**



3.3.2. Substitutia electrofila a hidrogenului in unele piridine substituite:

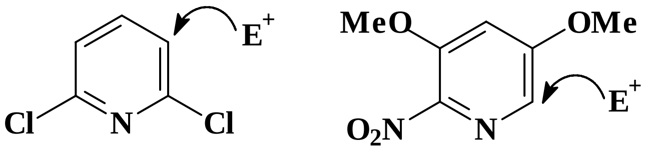
a) Nitrarea:

- importanta ca **sursa de aminopiridine (*via* reducere)**
- importanta ca **sursa de substraturi** care poseda un **presubstituent (-NO_2) labilizant**



Nota: nitrarea are loc cu **randamente satisfacatoare → bune**, in ordinea indicata mai sus.

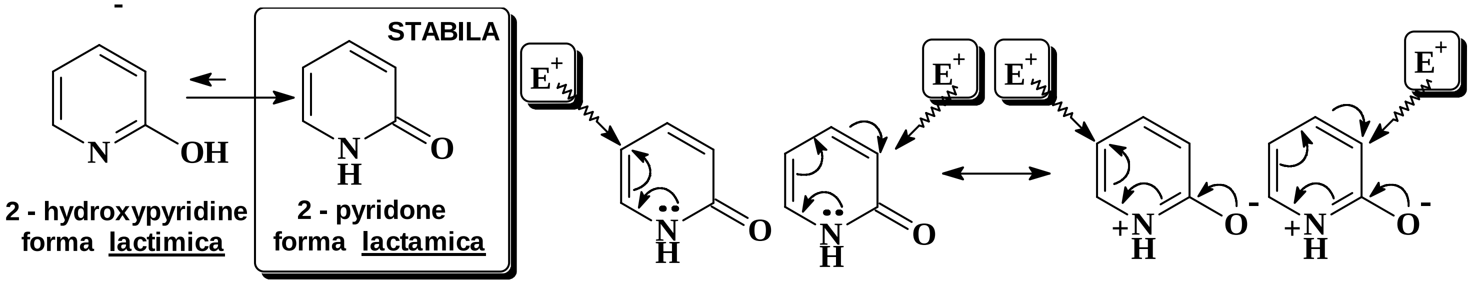
b) Orientari de interes general:

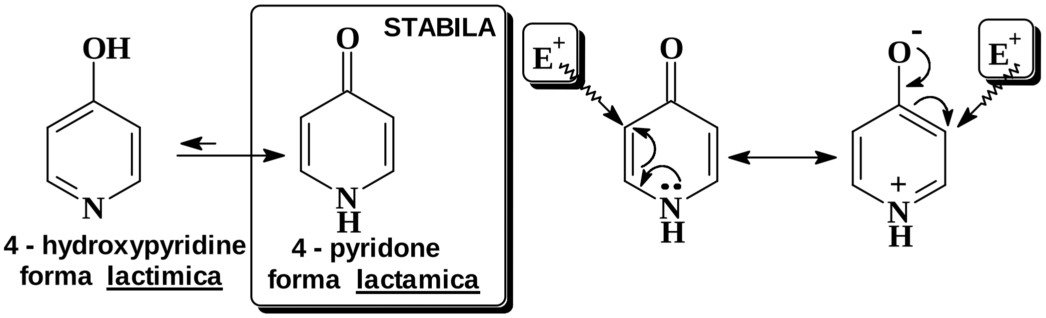


3.3.3. Abordarea substitutiei electrofile in seria piridinelor *via* 2 - si 4 – piridona

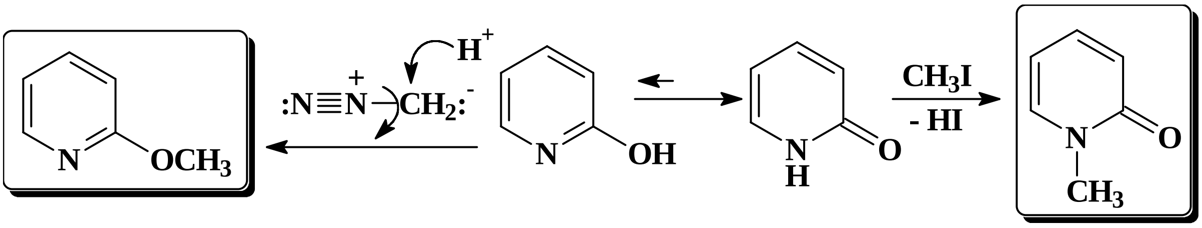
- compusii din titlu pot functiona, **datorita tautomeriei lactam – lactimica, drept substraturi activate** in directa reactiilor **SE**
- **pot**, de asemenea, **participa si la procese SN** (*e.g.* **clorurare**)
- **valoarea lor preparativa este similara *N* – oxizilor.**

- **orientarea substitutiei:**
-



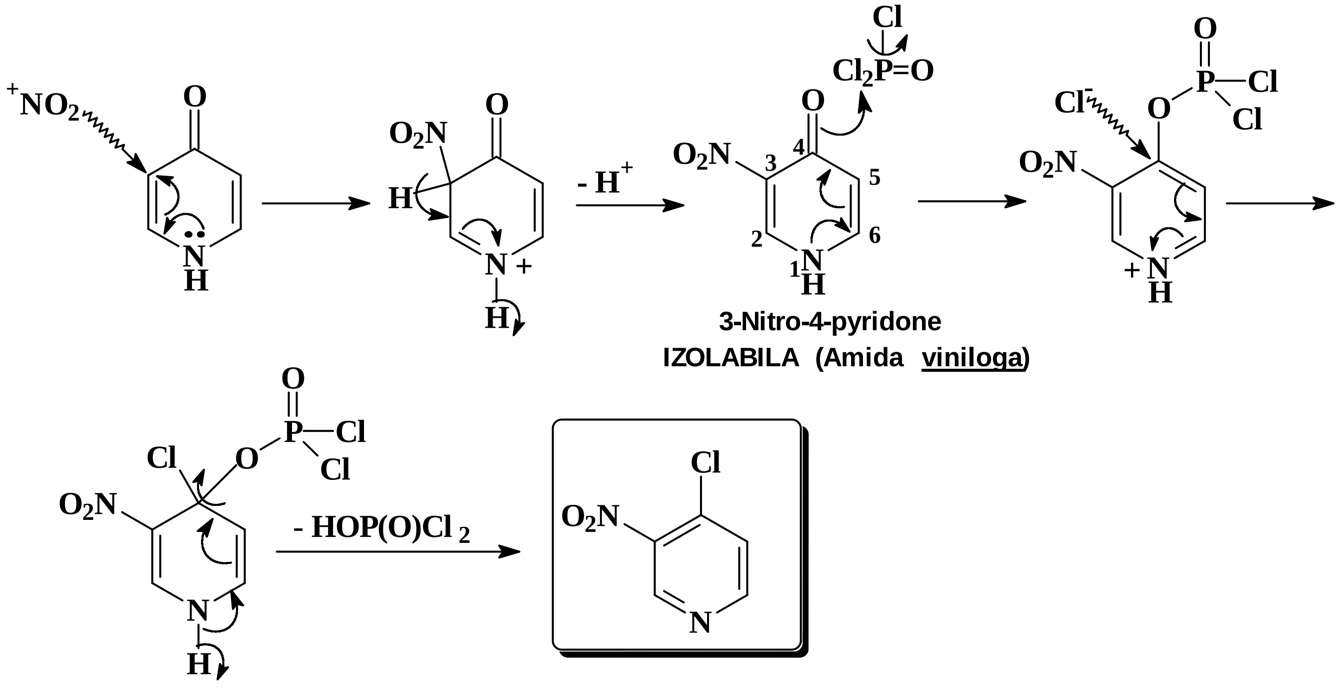


- **orientarea** este **totdeauna** ***"orto / para"*** fata de **oxigen (*"meta"*** fata de **azot)**
- in **stare solida**, existenta sub forma **tautomerilor lactamici** este **dovedita (RX)**
- **echilibrele** de mai sus sunt valabile in **solutie** unde prezenta **celor doi tautomeri** poate fi **pusa in evidenta**



- similar **piridin-*N*-oxizilor**, **grupa oxigenata** poate fi **substituita (optional)** pe cale **nucleofila** cu **clor**, sub actiunea **POCl$_3$**

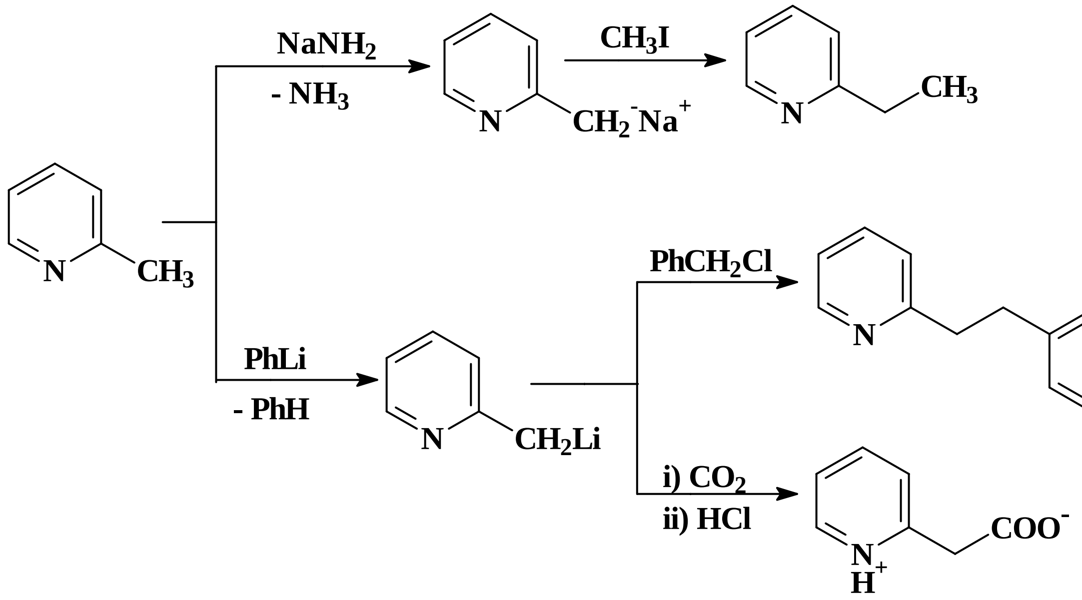
<u>Exemplu: prepararea 4-cloro-3-nitropiridinei</u>



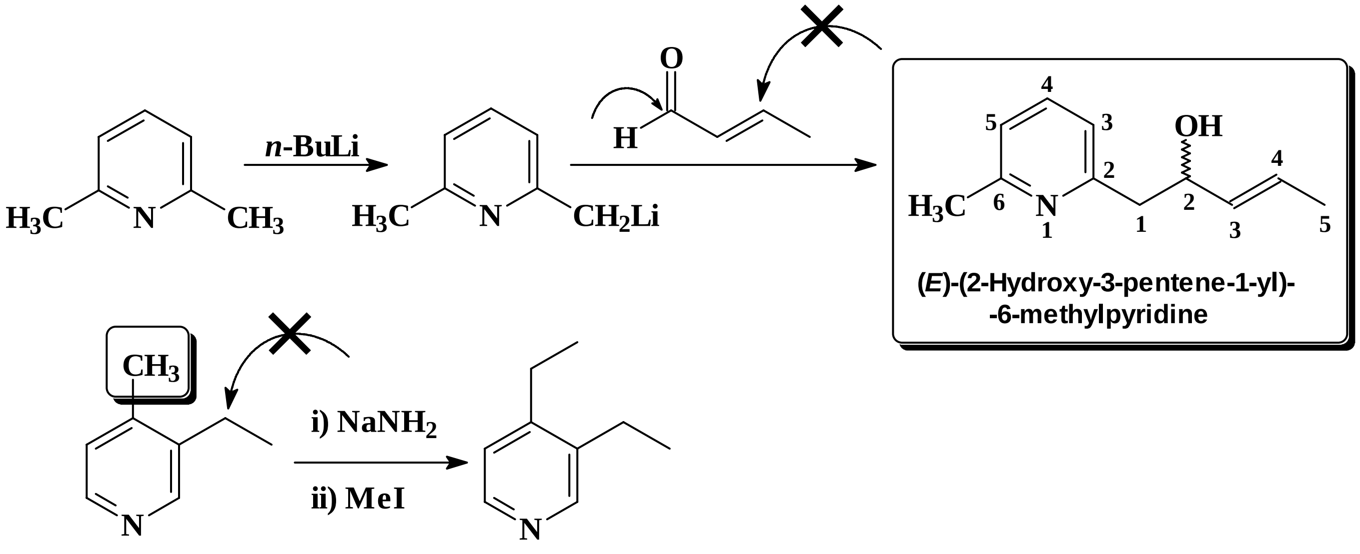
3.4. Functionalizarea prin metalare:

- **deprotonarea** sub actiunea **bazelor tari**, alcaline, **reuseste** mai ales asupra **grupelor metil de la C - 2, - 4, - 6** (analog unor **enamine mascate**)
- **deprotonarea** este **regioselectiva** in raport cu **pozitia 3 (nedeprotonabila)**
- **deprotonarea direct la ciclu** reuseste sub actiunea **$NaNH_2$ (Cicibabin)**
- deprotonarea sub actiunea ***n* - BuLi** la **ciclu nu reuseste** decat in prezenta unor **agenti chelatizanti** ai **metalului** (in caz contrar are loc polimerizarea litioderivatului)

Exemplul 1: functionalizarea 2 - metilpiridinei

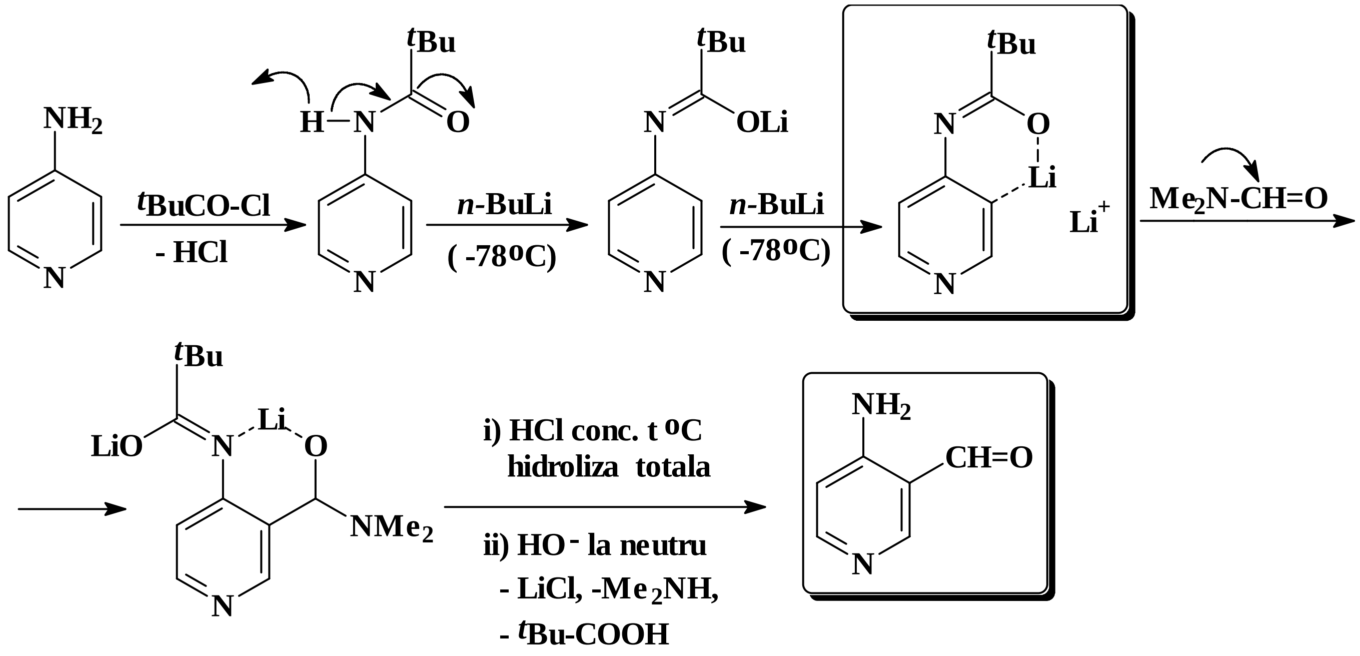


Exemplul 2: functionalizarea regioselectiva a unor dialchilpiridine



Nota 1: a se remarca **regioselectivitatea atacului nucleofil asupra aldehidei** α,β **- nesaturate**
Nota 2: a se remarca **faptul ca metilenul** de la ***C* - 3** ramane **neafectat**

Exemplul 3: metalare la ciclu cu *n* - BuLi *via* complexare



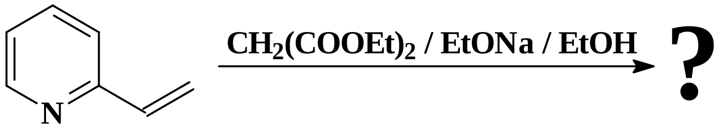
Nota 1: se prefera un reactiv de ***N* – acilare voluminos**, **usor de indepartat**

Nota 2: formilarea este **regioselectiva** deoarece are loc la ***C* – 3** si **nu la *O* amidic**

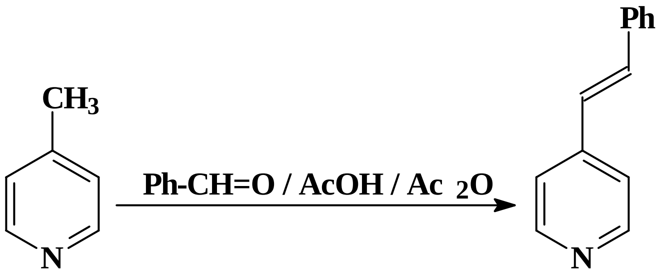
Nota 3: produsul final manifesta suficienta stabilitate pentru a fi izolat (mai ales ca **clorhidrat**)

P – 6

P-6.1. Ce se formeaza in reactia de mai jos si care este mecanismul ei ?



P-6.2. Dati mecanismul reactiei de mai jos, care are loc cu implicarea anhidridei acetice:



P-6.3. Precizati modul de formare a lactonei de mai jos: