INDOLES AND RELATED STRUCTURES

1. General

a) Typical representatives
b) Aromatic character
c) NMR data
d) Acid-base character and tautomerism of indole
e) Annular elementotropy

2. Syntheses

2.1. Syntheses of indoles

2.1.1. *Fischer* synthesis
2.1.2. *Leimgruber* synthesis
2.1.3. Derivatives of 5,6-dihydroxyindole as precursors of melanine, the black pigment of human hair
2.1.4. *Reissert* synthesis

2.2. Syntheses of benzo-heteroanalogues

2.2.1. *Bischler* general synthesis of *C*-3-substituted indoles, benzothiophenes and benzofurans
2.2.2. Synthesis of indazoles
2.2.3. Synthesis of benzotriazole
2.2.4. Synthesis of benzoazoles with two heteroatoms in positions 1, 3

3. Functionalisation of indoles

3.1. Functionalisation by electrophilic substitution

a) *Mannich* reaction and further functionalisations
b) *Vilsmeier* reaction and applications
c) Acylation at C-3
d) Electrophilic substitution at C-3 with stabilisation of the 3*H*-indolic form

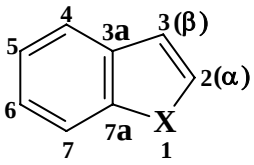
3.2. Functionalisation by electrophilic substitution *via* metallation

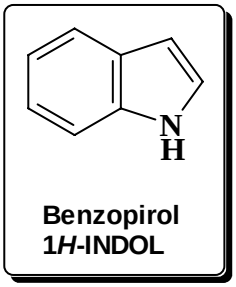
Modifications (improvements, additions, corrections, up to dates *etc.*) are subjected to no notice.

INDOLI SI STRUCTURI INRUDITE

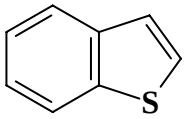
1. Generalitati:

a) reprezentanti tipici:

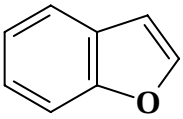




Benzopirol
1*H*-INDOL



Benzotiofen
TIONAFTEN

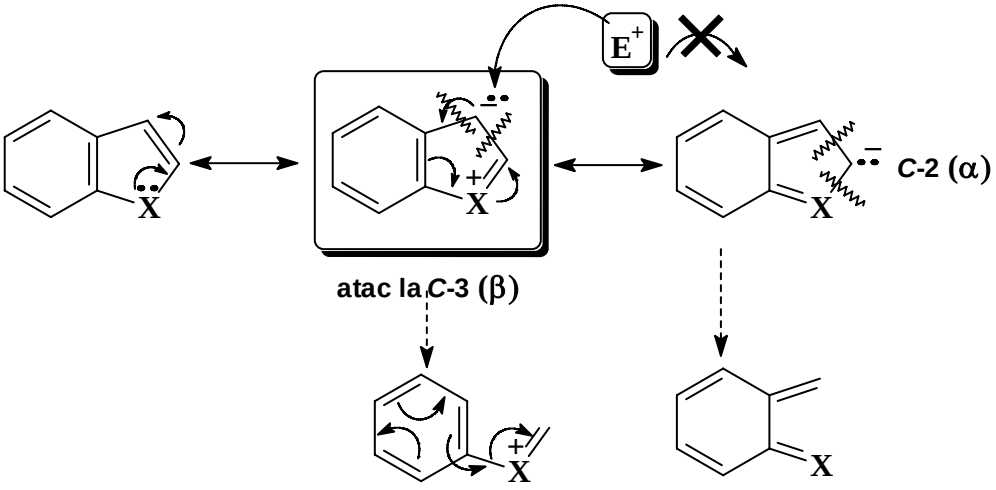


Benzofuran
CUMARONA

- provin, **formal,** din condensarea benzenului cu pentahetarenele corespunzatoare
- in denumire, condensarea se exprima prin utilizarea prefixului ***benz(o)*: <u>benz</u>imidazol**, **<u>benz</u>izoxazol**, **<u>benzo</u>tiazol, <u>benzo</u>triazol,** etc.
- **importanta indolilor** o **depaseste considerabil** pe cea a analogilor cu oxigen si sulf.

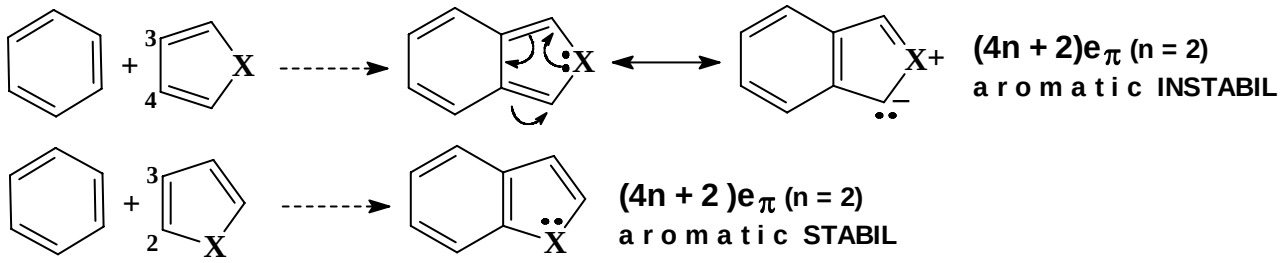
b) caracterul aromatic:

- sisteme delocalizate cu **10eπ** → caracter aromatic **mai accentuat** fata de pentahetarene.
  → diferenta de **reactivitate mai mare** intre pozitiile **C - 2 *vs.* C - 3** in reactiile **SE** decat in cazul analogilor pirol, tiofen si furan
  → **regioselectivitati net superioare**



Alte consecinte:

- sunt **relativ instabile** structurile in care condensarea inelelor se face la catena ***C* - 3 + *C* – 4 (in loc de *C* – 2 + *C* – 3)** (numerotarea pentaheterociclului)



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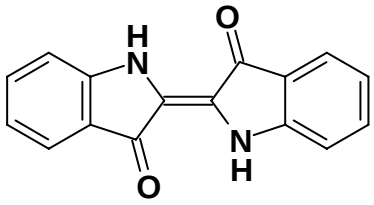
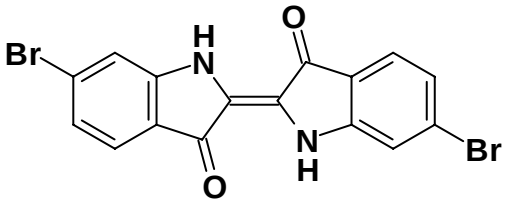
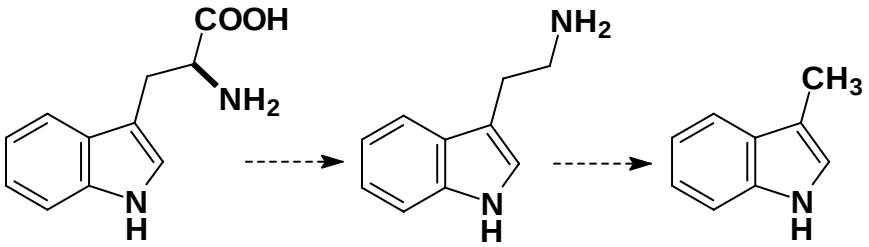


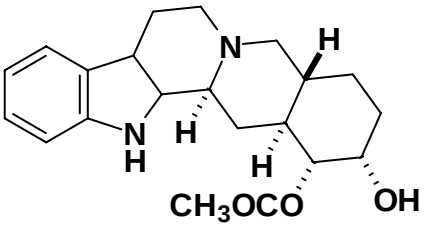
indigo



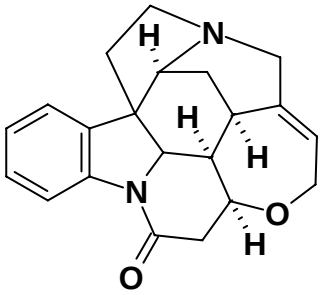
6,6'-dibromoindigo
Tyrian purple



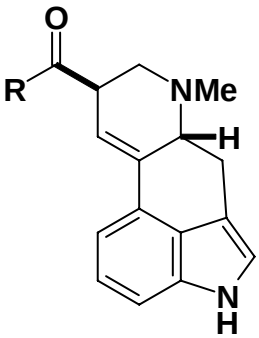
***S*-tryptophan** **tryptamine** **skatole**



yohimbine



strychnine



R = H, Lysergic Acid
R = Net_2, Lysergic Säuere Diäethylamid,

L S D

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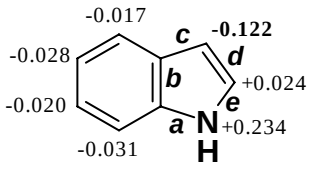
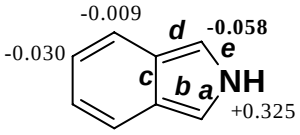
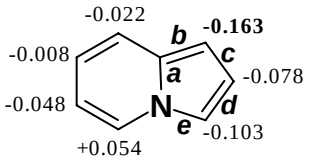
Estimated π-charges in benzopyrroles:



benzo[*b*]pyrrole
Indole



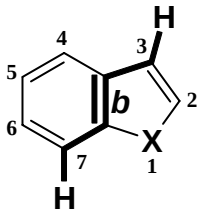
benzo[*c*]pyrrole
isoindole



benzo[*a*]pyrrole

c) NMR-data

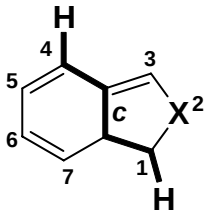
^{1}H-NMR Spectral data for benzo[b] heterocycles: δ (ppm); ^{n}J (Hz)



X = NH, O, S, Se, Te

	X = NH	X = O	X = S	X = Se	X = Te
H-2	6.52 – 7.27	7.52 – 7.78	7.33	7.90	8.65
H-3	6.29 – 6.45	6.66 – 6.76	7.22	7.50	7.91
H-4	7.55	7.49 – 7.63	7.72	7.76	7.79
H-5	7.00	7.13 – 7.23	7.26	7.19 – 7.29	7.08 – 7.30
H-6	7.08	7.19 – 7.30	7.24	7.19 – 7.29	7.08 – 7.30
H-7	7.40	7.42 – 7.51	7.79	7.86	7.90
$^{3}J_{2,3}$	3.1	2.19	5.5	6.0	7.10
$^{6}J_{2,6}$	-	-	0.5	0.3	-
$^{5}J_{3,7}$	**0.7**	**0.87**	**0.75**	**0.67**	**-**
$^{3}J_{4,5}$	7.8	7.89	8.5	-	-
$^{4}J_{4,6}$	1.2	1.28	1.14	-	-
$^{5}J_{4,7}$	0.9	0.80	0.7	-	-
$^{3}J_{5,6}$	7.0	7.27	7.0 - 7.5	-	-
$^{4}J_{5,7}$	1.2	0.92	0.5 - 1.0	-	-
$^{3}J_{6,7}$	8.0	8.43	8.0 - 7.5	-	-

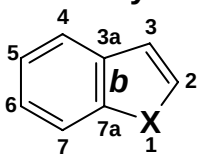
^{1}H-NMR Spectral data for benzo[*c*] heterocycles: δ (ppm); ^{n}J (Hz)



X = NH, O, S, Se

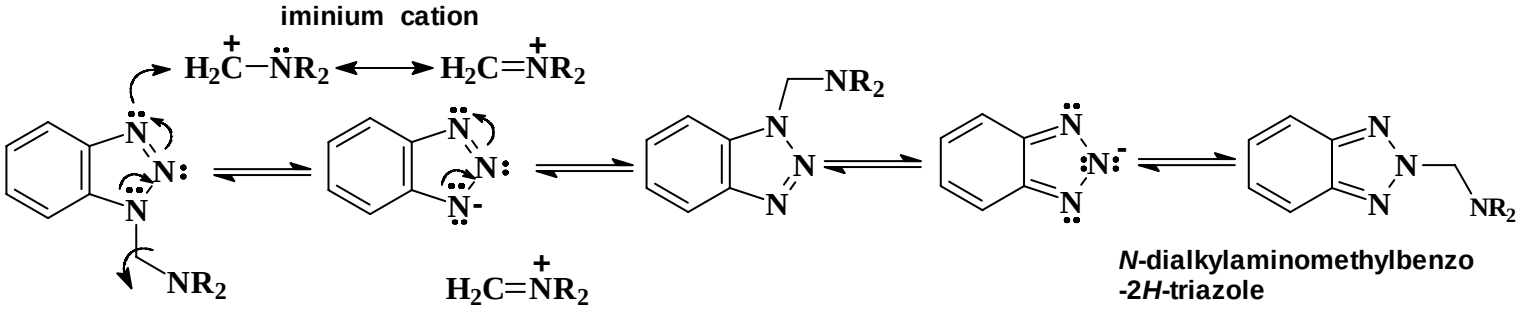
X	H-1, -3	H-4, -7	H-5, -6	$^{5}J_{1,4}$	$^{3}J_{4,5}$	$^{4}J_{4,6}$	$^{5}J_{4,7}$	$^{3}J_{5,6}$
NH	6.28	7.50	6.80	**-**	8.49	-	-	6.29
O	7.99	7.38	6.84	**0.64**	8.52	1.01	0.57	6.22
S	7.63	7.59	7.04	**0.42**	8.64	1.03	0.79	6.36
Se	8.40	7.33 – 7.54	6.77 – 7.02	**-**	9.16	-	-	6.79

^{13}C-NMR Spectral data for benzo[*b*] heterocycles: δ (ppm)



	X = NH	X = O	X = S
C-2	124.67	145.1	126.21
C-3	102.14	106.9	123.79
C-4	120.76	121.6	123.57
C-5	121.81	123.2	124.10
C-6	119.76	124.6	124.17
C-7	111.35	111.8	122.44
C-7a	135.65	155.5	139.71
C-3a	128.26	127.9	139.57

e) Annular Elementotropy: isomerism involving reverse migration of organic and inorganic groups heavier than proton. It is <u>*intermolecular*</u>. It is **not** a <u>*rearrangement*</u> (intramolecular). Annular elementotropy is: alkylotropy (R); acylotropy (R-CO-); sililotropy (-$SiMe_3$); metallotropy (-SnR_3).



***N*-dialkylaminomethylbenzo -1*H*-triazole**

***N*-dialkylaminomethylbenzo -2*H*-triazole**

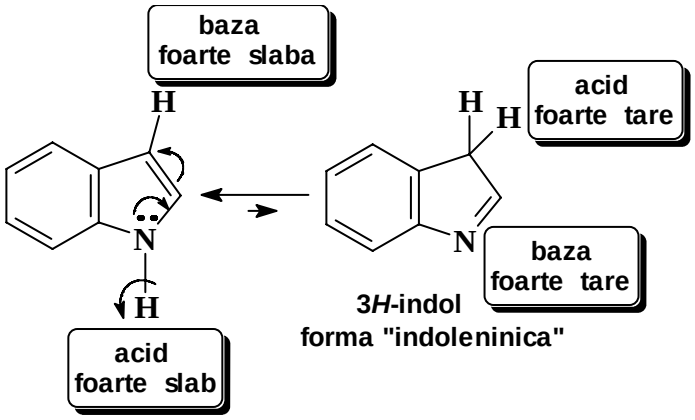
in solid state: 100% 1*H*

in polar solvents: dominant 1*H*

in non polar solvents: 1:1 1*H vs.* 2*H*

d) caracterul acido - bazic si tautomeria indolului:

- ca atare, acid foarte slab la **N*H*** (pKa cca. 17) si baza foarte slaba la ***C* - 3**.



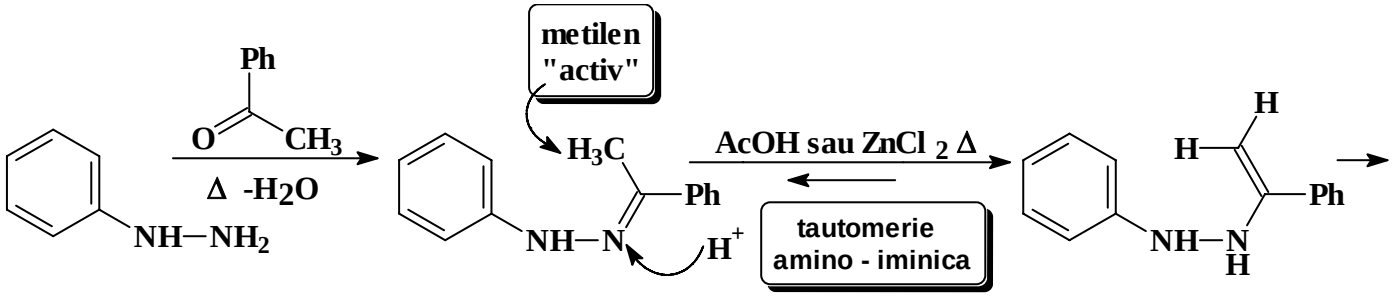
- **forma indoleninica *ca atare*** poate sa apara doar in ambianta de reactie; se cunosc insa **forme substituite, stabile**, ale acesteia.

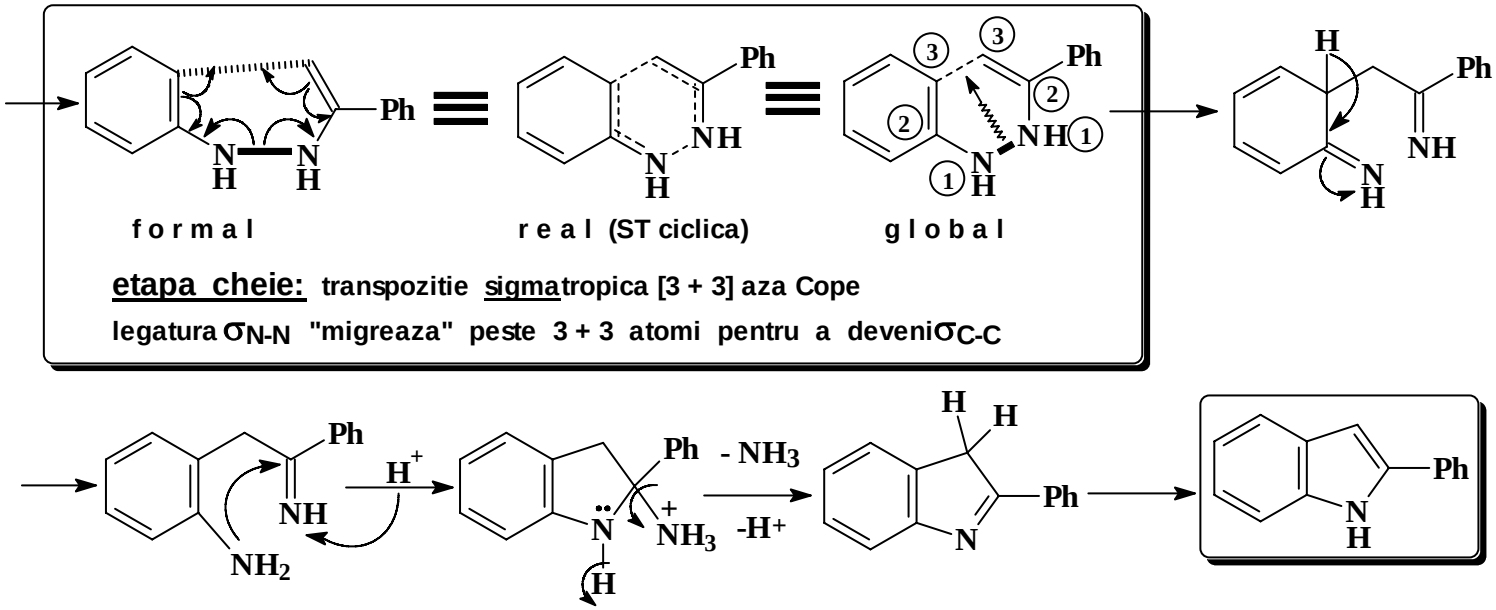
2. Sinteze:

2.1. Sinteze de indoli:

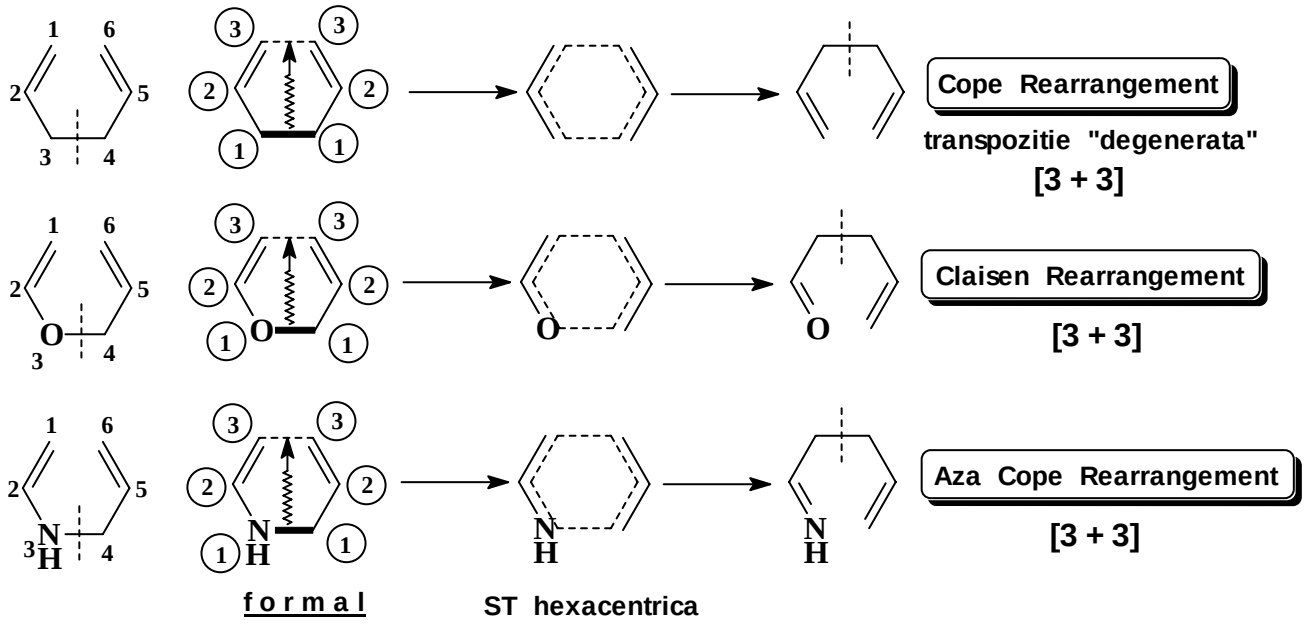
2.1.1. Sinteza Fischer

- **obiectiv:** prepararea de **indoli C - 2, - 3 mono-** sau **disubstituiti** fara a afecta inelul aromatic
- **esenta metodei: transpozitie diaza Cope a unei hidrazine *N,N'* – disubstituite**





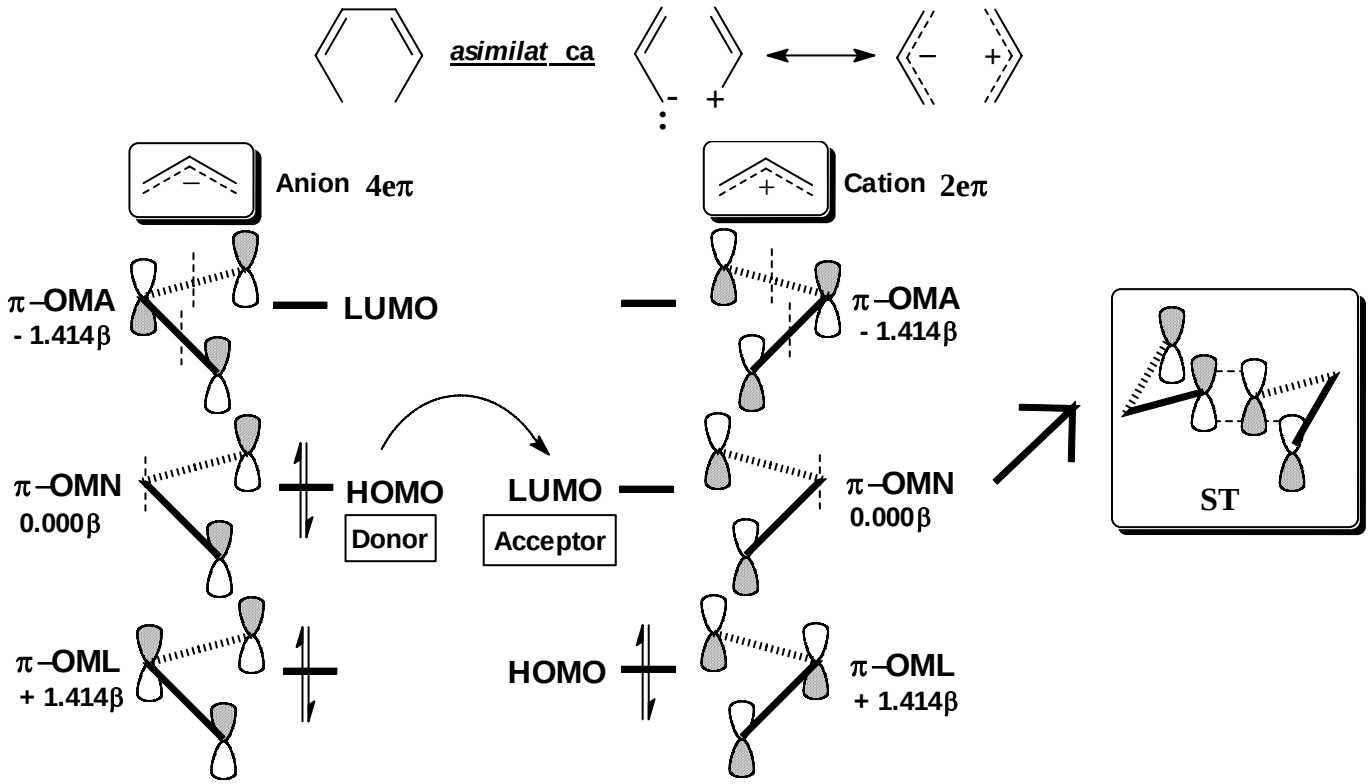
Nota 1: etapa cheie are **valabilitate generala** pentru sinteze **e l e c t r o c i c l i c e** de tipul:



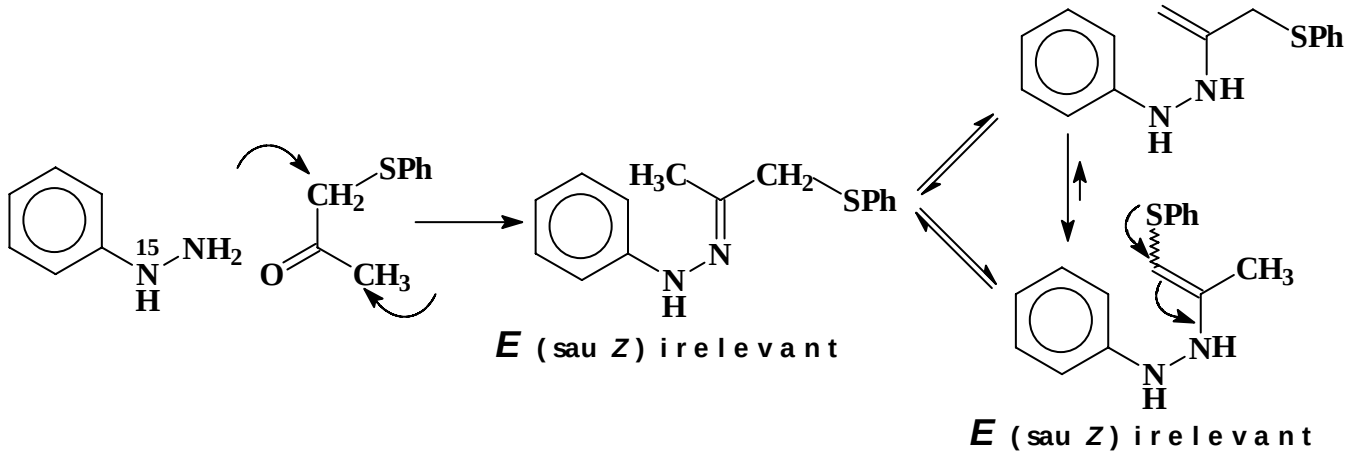
- toate procesele de acest tip **sunt procese electrociclice permise** de catre **simetria orbitalilor moleculari**; au loc la cald (sunt **permise termic**)
- oricare produs de plecare poate fi descompus, **formal**, in **doua unitati (de tip) alil**
- **modele ale starii de tranzitie: 2 concepte**

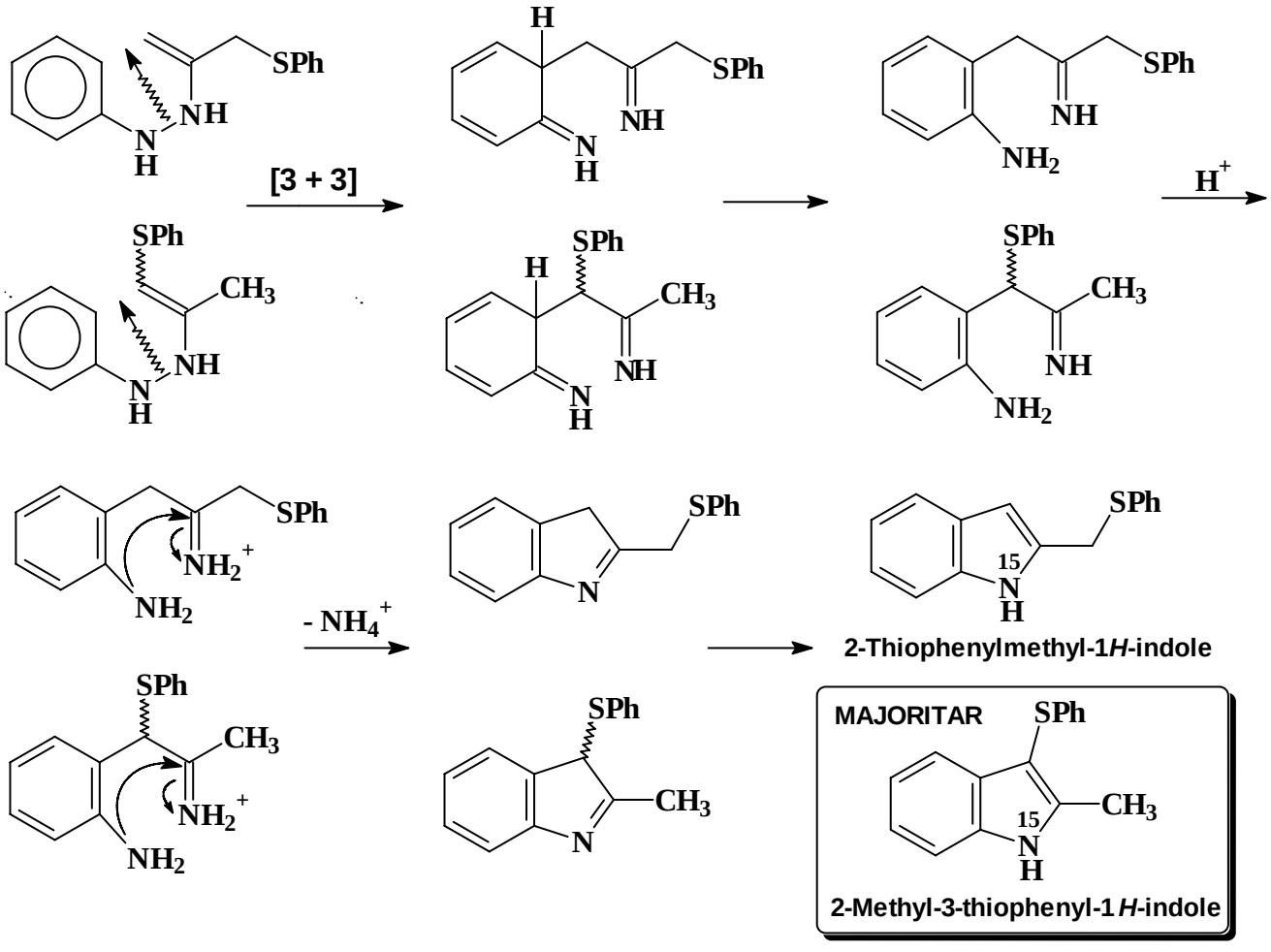
i) ***stare de tranzitie de tip aromatic (Huckel):***

ii) cicloaditie [4 + 2]e_π intre anionul respectiv cationul alil



Nota 2: in cazul **cetonelor** care poseda **2 (doi) metileni enolizabili neechivalenti** apar probleme de **riegioselectivitate a ciclizarii → se formeaza cu preponderenta indolul care provine din hidrazina cu <u>dubla legatura etilenica cea mai substituita</u>**





Nota 3: sintezele efectuate cu **hidrazina marcata izotopic (^{15}N)** si izolare de derivati diiminici (protonati) confirma mecanismul

Nota 4: partenerul carbonilic poate fi o aldehida sau o cetona care poseda **cel putin un metilen enolizabil**; ele sunt de forma **$RCOCH_2R'$ (R = H, alchil <u>superior Me</u>, aril)**

Nota 5: sunt cunoscute si cazuri in care **catalizatorul nici nu este necesar,** doar **inalzirea (peste 100^{o}C)**

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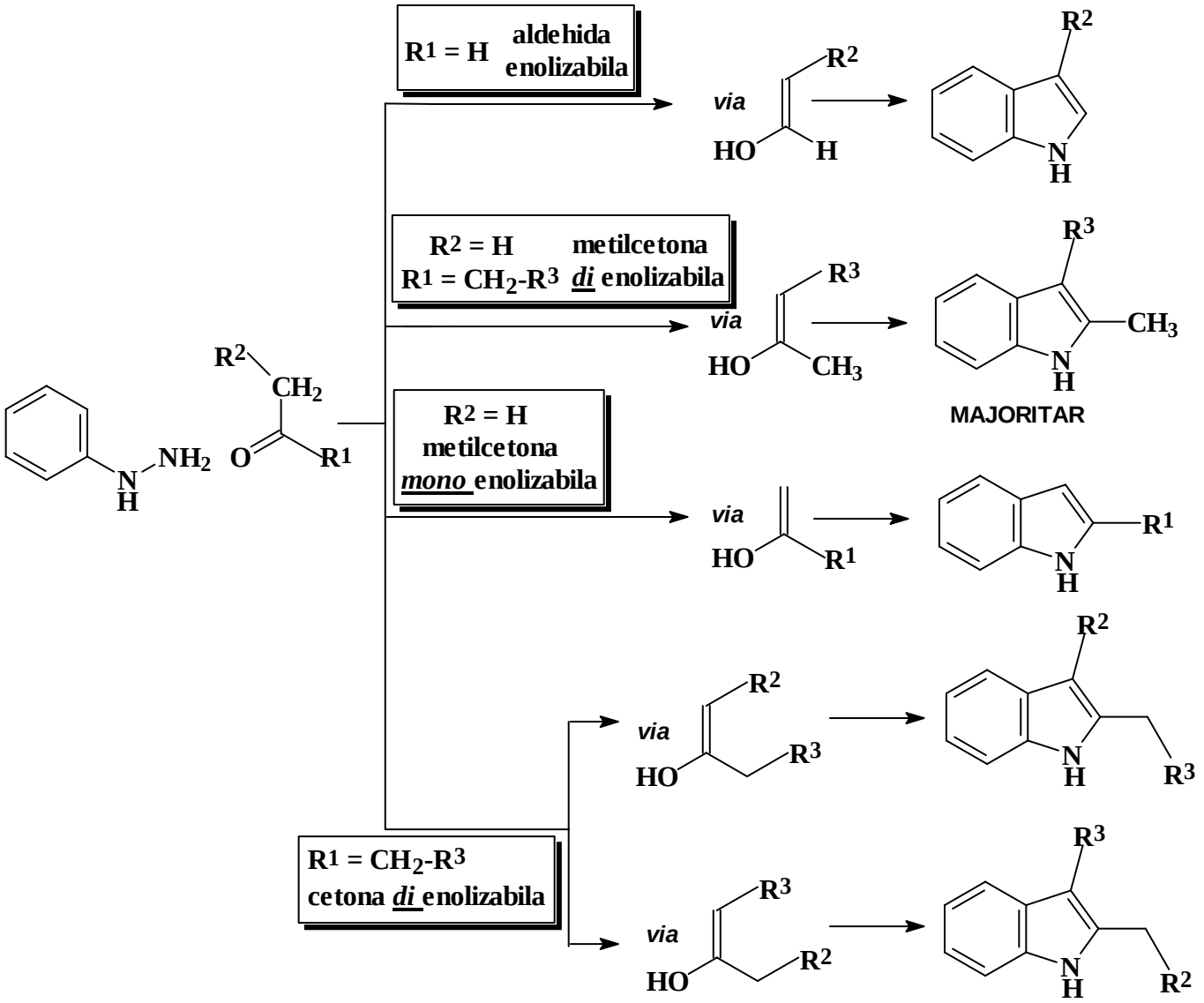
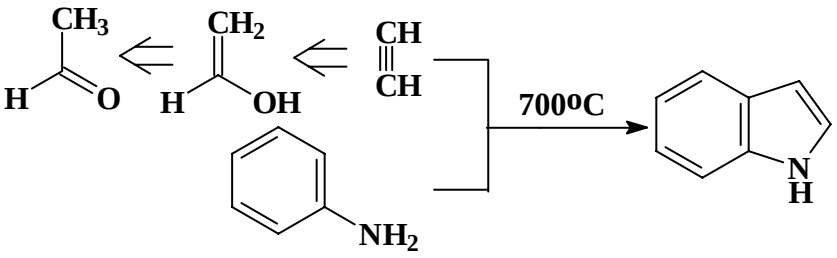
Generalizarea metodei:

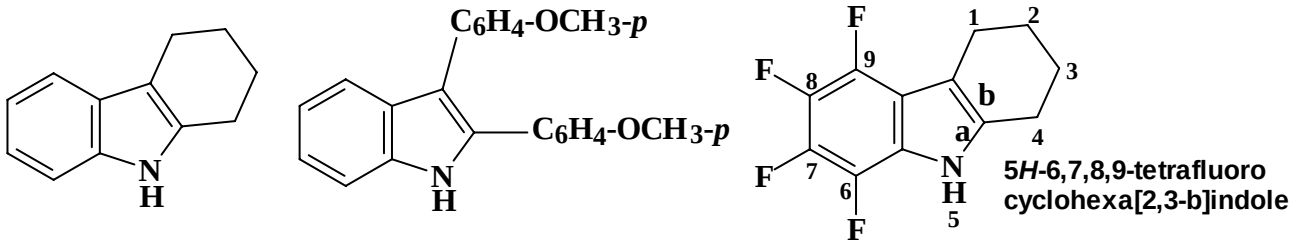


Obs. 1: pentru **acetaldehida** (→ indolul ***ca atare***) se prefera alte metode sau sinteza din **echivalenti sintetici**



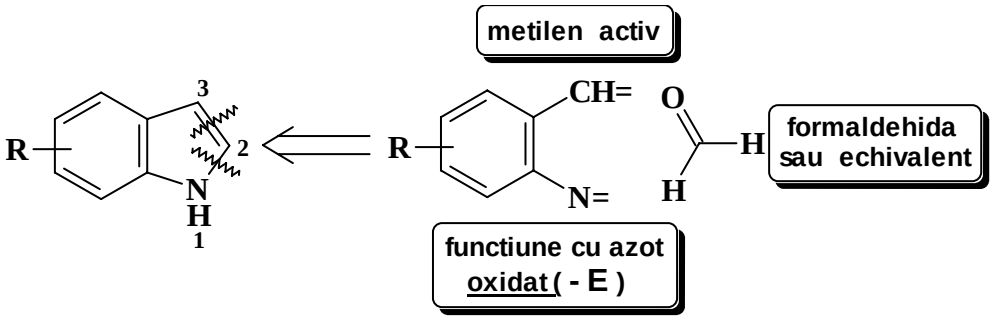
Obs. 2: fenil hidrazina (inelul aromatic **monosubstituit sau cu HOMO de joasa energie)** este **cea mai apta** de a da transpozitia sigmatropica diaza Cope

Obs. 3: metoda Fischer furnizeaza **indoli *C* - 2, - 3 mono- si / sau disubstituiti: exemple**

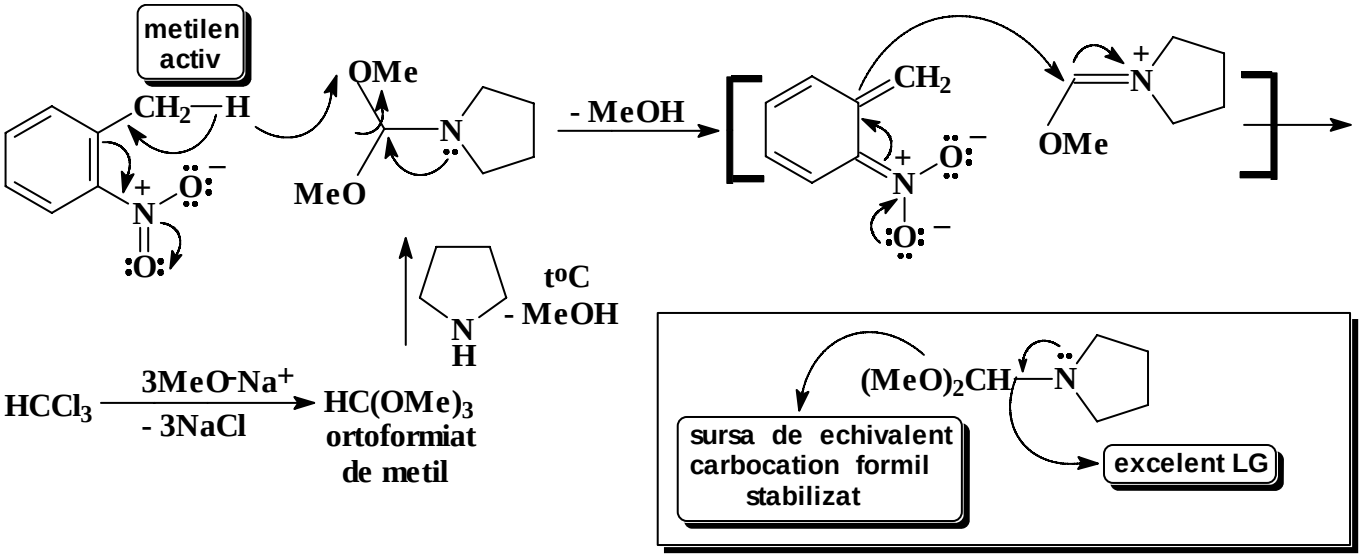


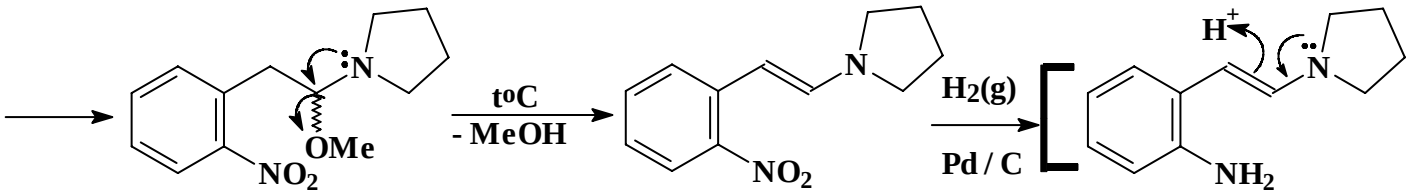
2.1.2. Metoda *Leimgruber*:

- **obiective:** prepararea de **indoli nesubstituiti** in **partea pirolica** dar **substituiti** pe **inelul benzenic**
- **principiul metodei:** se construieste secventa **C – 2 – C - 3** prin aport de **echivalent formil stabilizat de un inel pirolidinic (a se compara cu reactivul *Vilsmeier*)**
- **deconectare de tipul:**

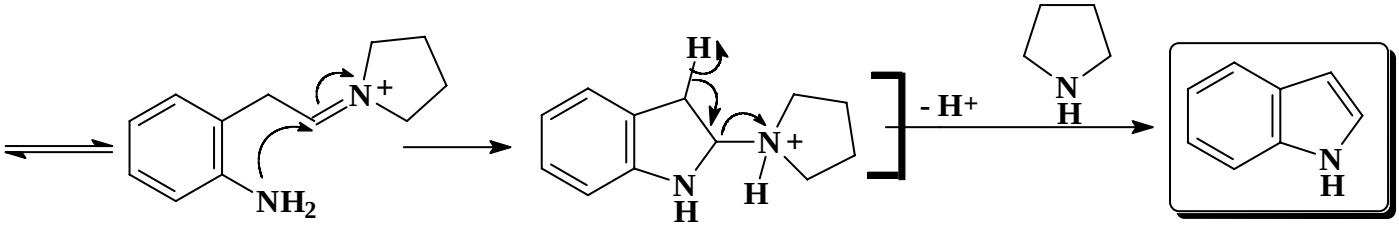


Exemplu: sinteza indolului ca atare

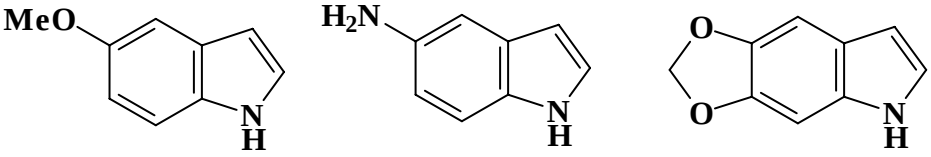




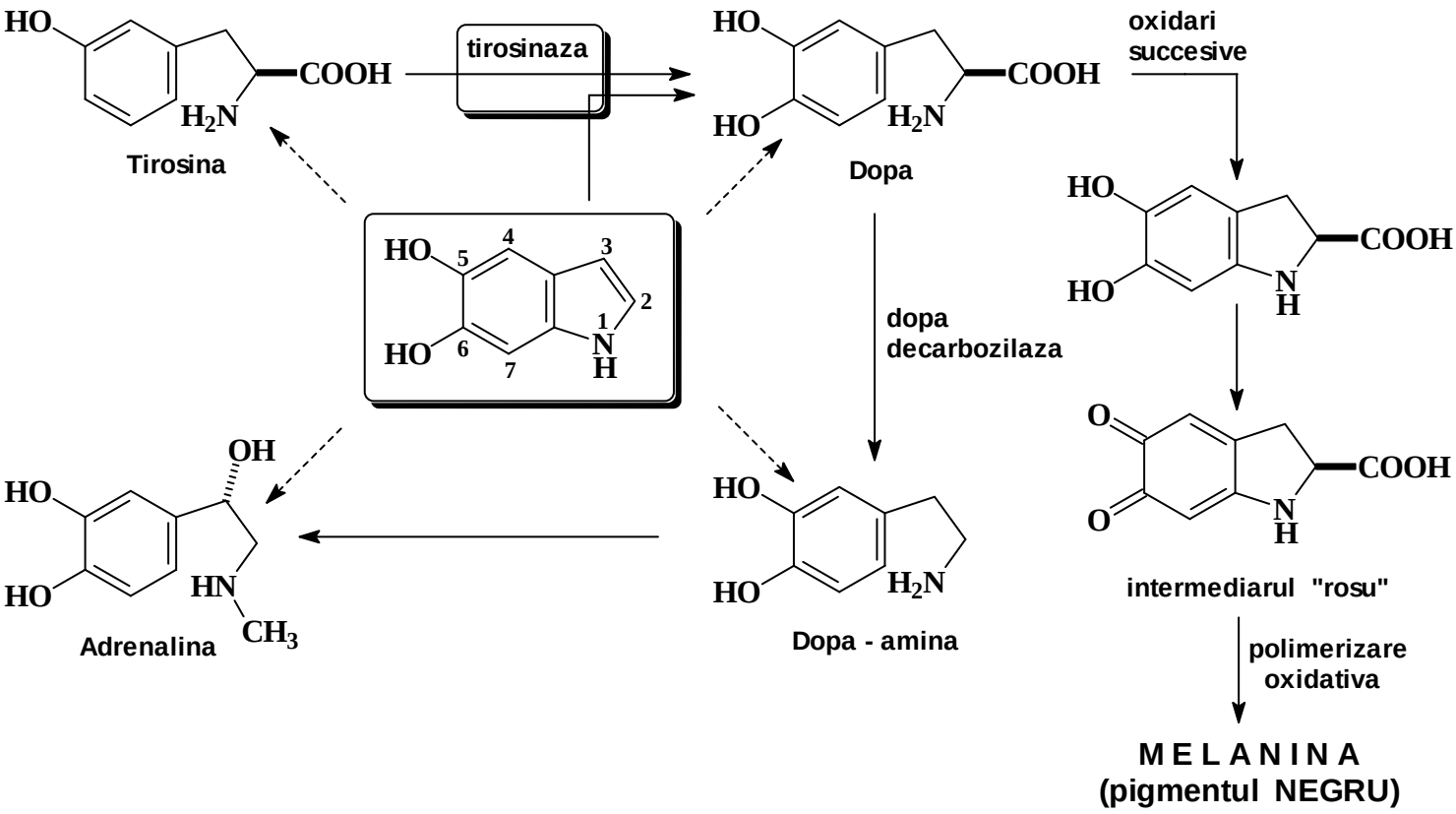
E **enamina**
(configuratia este i r e l e v a n t a)



Indoli accesibili prin metoda *Leimgruber*:



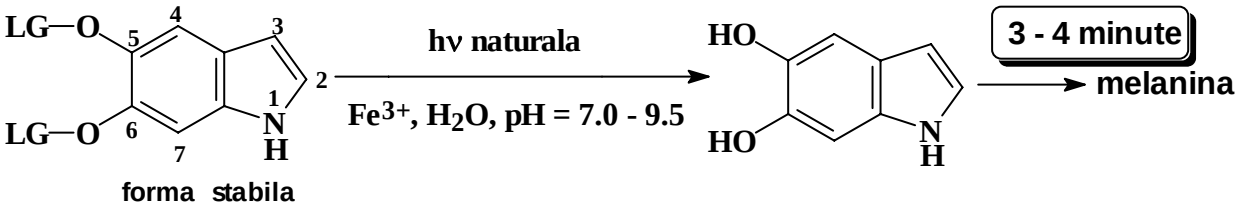
2.1.3. Derivati ai 5,6-Dihidroxiindolului: ca precursori ai melaninei, pigmentul negru al parului organismelor vii



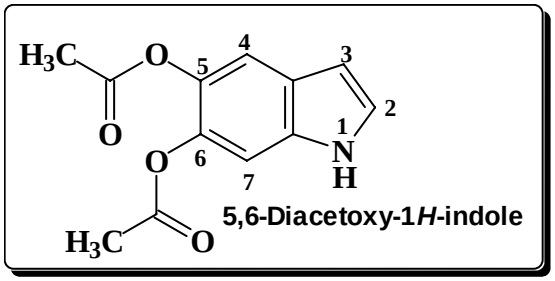
i) Problema: inlocuirea colorantilor pentru par sintetici ("traditionali") cu **precursori** ai **melaninei naturale** (eventual modificata prin substituire potrivita)

ii) Dificultatea problemei: 5,6-dihidroxiindolul **este foarte instabil (oxidabil)** si **inutilizabil** ca atare

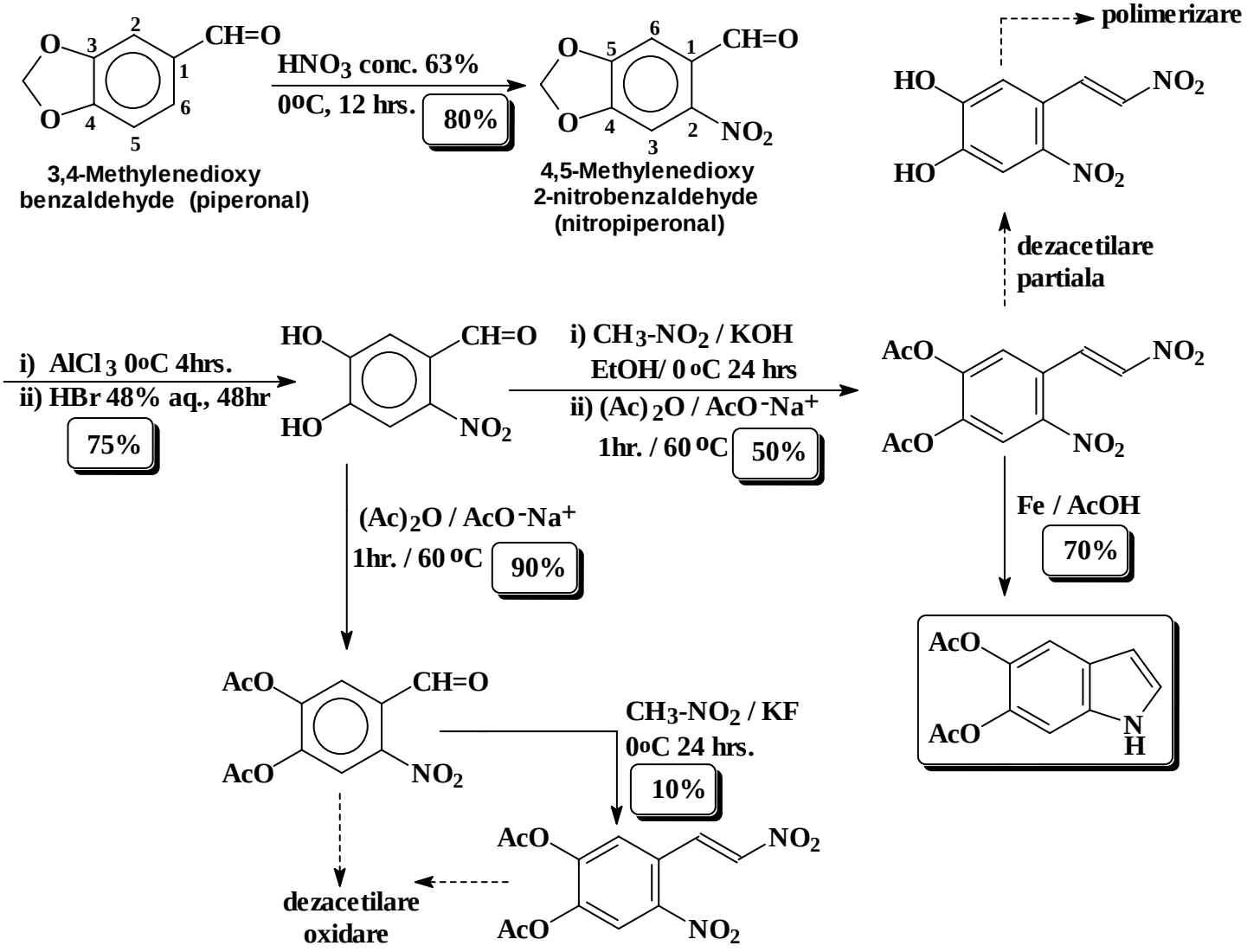
iii) Solutia problemei: prepararea de forme ***O* – 5, - 6 – diprotejate** care **sa hidrolizeze** la **pH-ul organismului, la temperatura ambianta** si susceptibile de a suferi un proces de **polimerizare oxidativa controlata**



<u>In functie de natura LG se poate imagina o gama foarte larga de compusi</u>



L'Oréal Paris® ; Procter & Gamble®



Nota 1: sinteza este **unicat** prin aceea ca porneste de la o structura aromatica ***orto*** **disubstituita** cu **doua grupari oxidate (electronoatragatoare)**

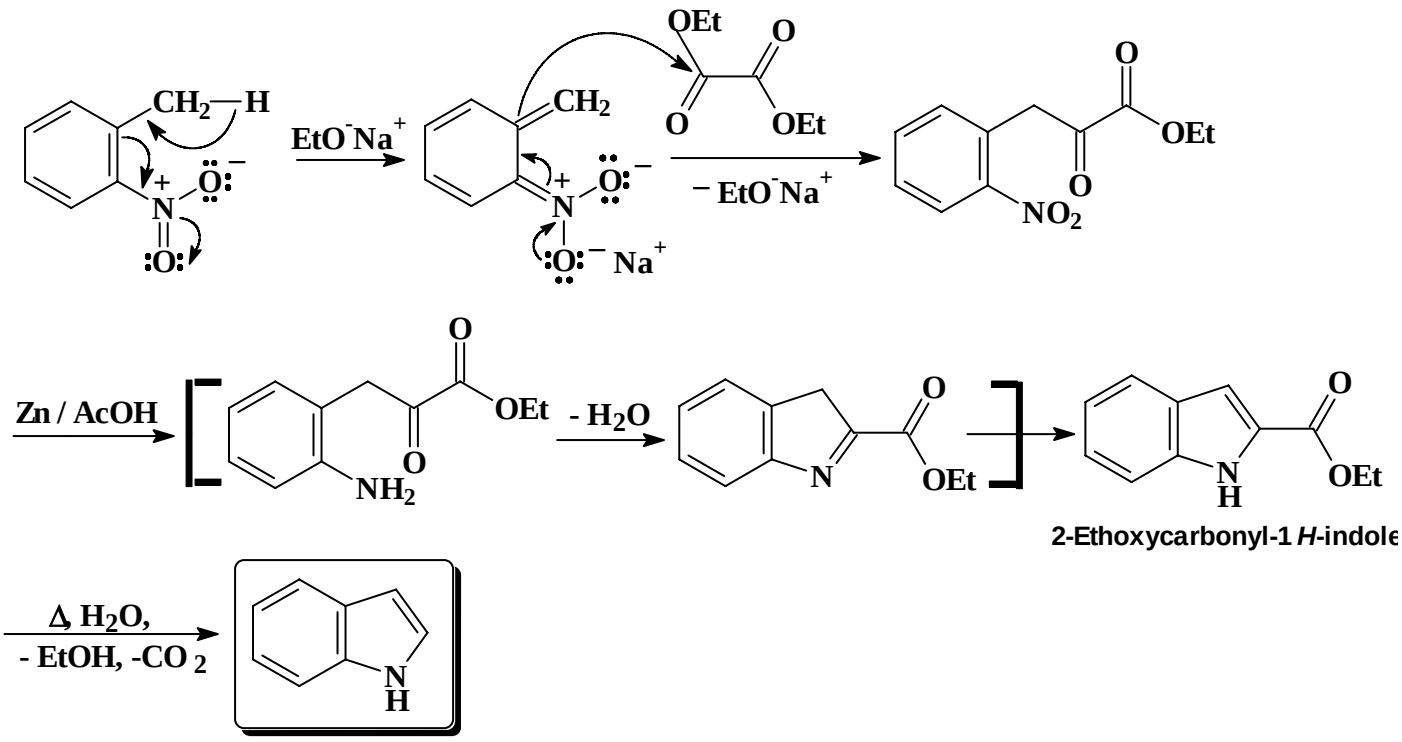
Nota 2: **toti precursorii diacetilati** manifesta **instabiliate** in **directia hidrolizei**

Nota 3: **alte grupe protectoare** ale hidroxililor fenolici **nu sunt oportune** din cauza **impedimentelor sterice** care **impiedeca penetrarea** compusului in **interiorul firului** unde ***apoi*** are loc **hidroliza** si **polimerizarea oxidativa**

Nota 4: protejarea hidroxililor fenolici ca **heterociclu 1,3 - dioxolenic** este **foarte stabila**

2.1.4. Sinteza *Reissert*:

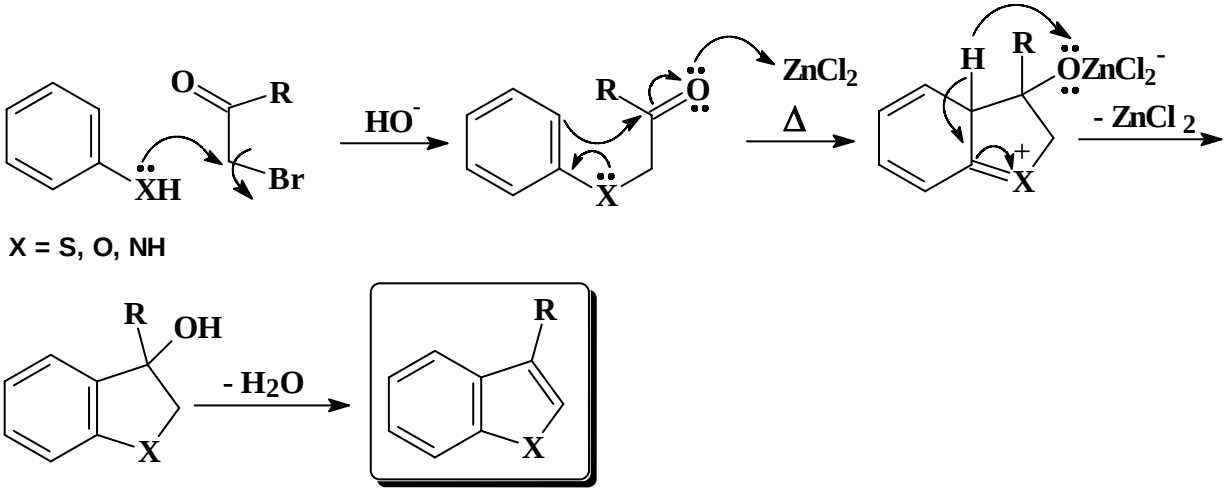
- **obiectiv:** sinteza indolului ca atare



Nota: metoda **similara variantei *Leimgruber***, fragmentul **formil** este adus ca **ester oxalic** dupa care **restul activant etoxicarbonil este indepartat.**

2.2. Sinteze de benzo heteroanalogi

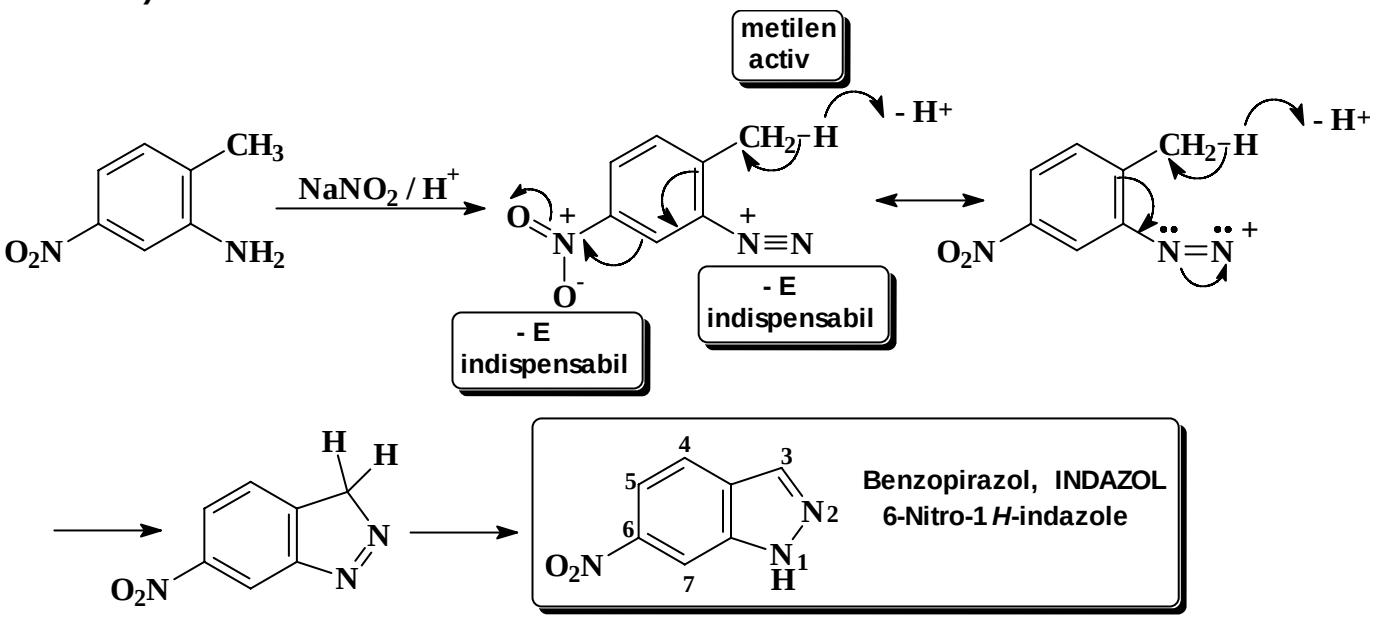
2.2.1. Sinteza generala *Bischler* pentru Indoli, Benzotiofeni si Benzofurani *C* - 3 substituiti



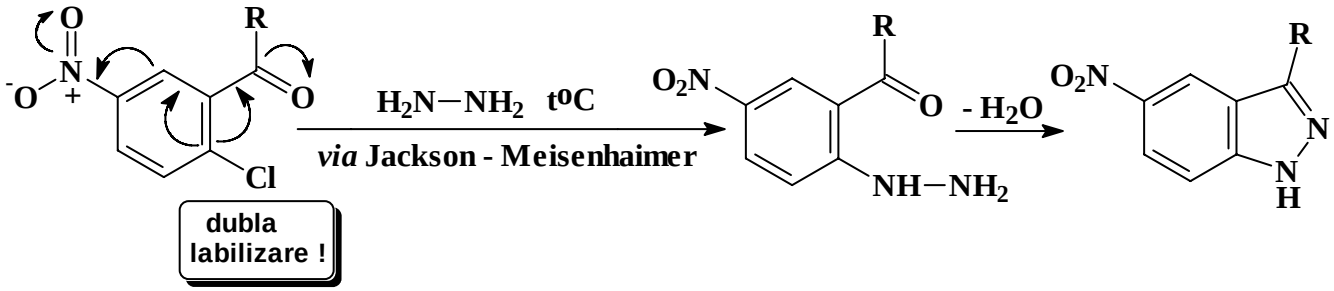
Nota: valabilitatea metodei depinde de **accesibilitatea convenabila** a **α - bromocetonelor deoarece regioselectivitatea α - bromurarii cetonelor dienolizabile scade astfel: >CH- > -CH_2- > -CH_3**

2.2.2. Sinteze de indazoli (benzopirazoli):

a) *via* sare de diazoniu

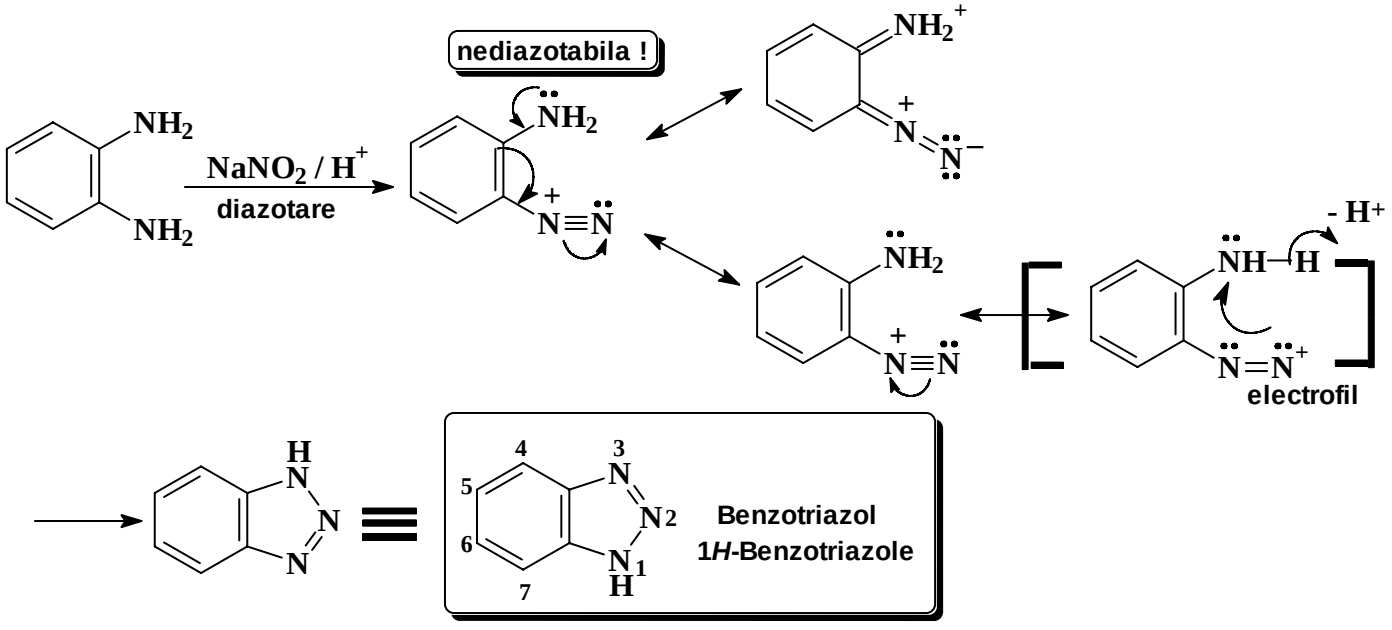


b) *via* SN_2Ar cu nucleofilul avand legatura *N - N* preformata



Nota: metode **particular performante** deoarece sunt prezenta **doua grupe activatoare**

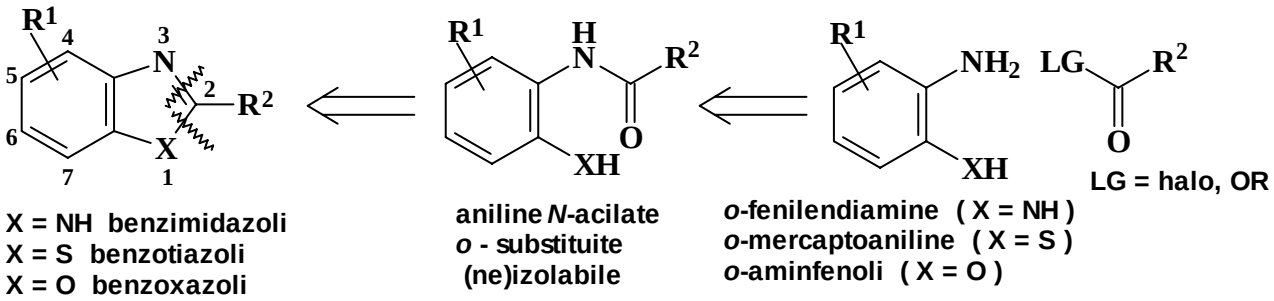
2.2.3. Sinteza benzotriazolului:



Nota: ciclizare **spontana**; **sarea de diazoniu nu este izolabila**

2.2.4. Sinteze de benzoazoli cu doi heteroatomi in pozitii 1,3:

- **deconecatre hidrolitica: (1 – 2) – (2 – 3)**



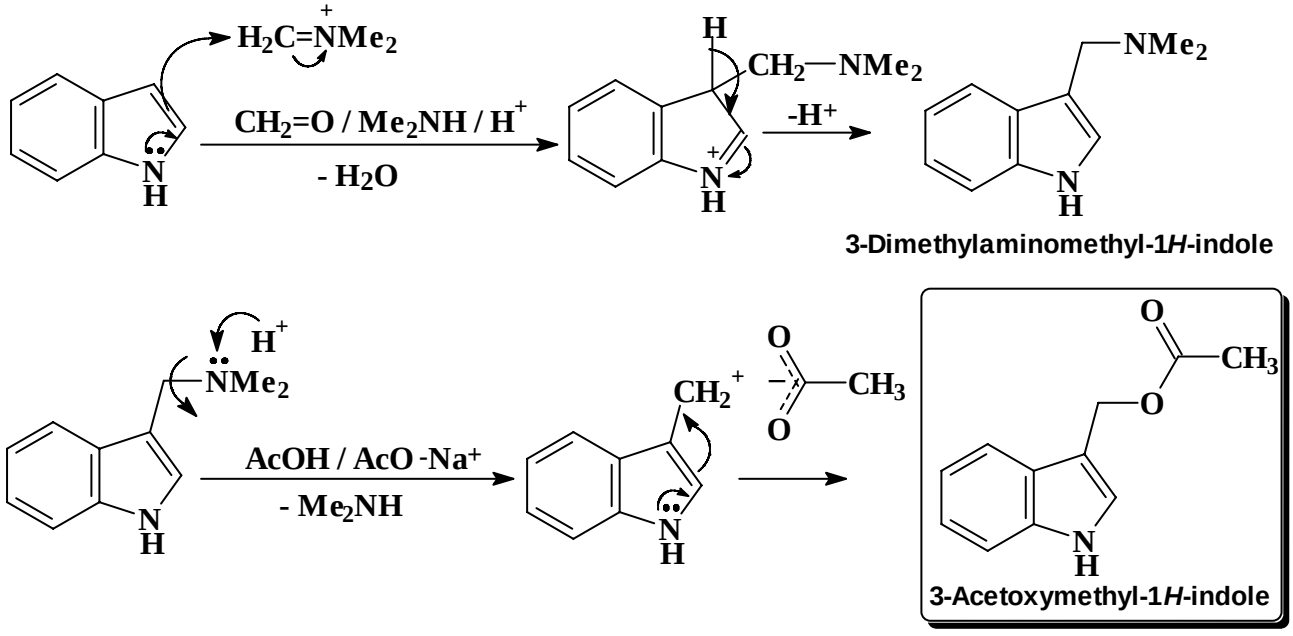
3. Functionalizarea indolilor

3.1. Functionalizarea prin SE

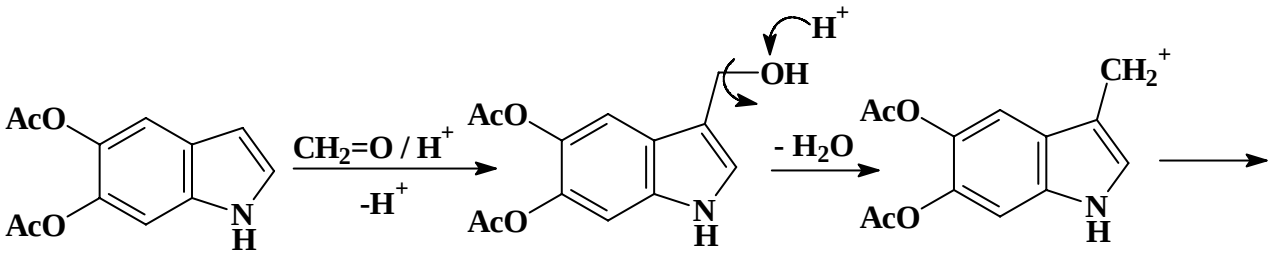
Generalitati:

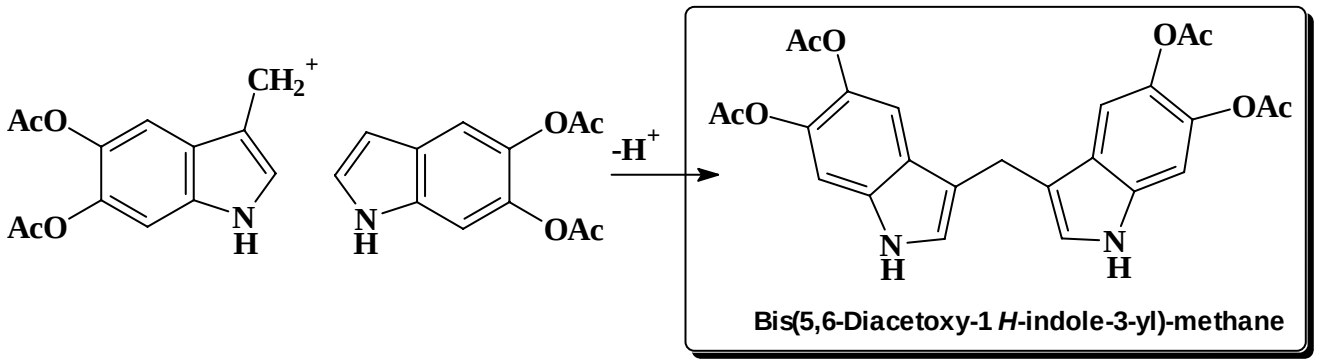
- **reactivitatea generala** trebuie privita ca **superioara pirolului** si **analoaga unei enamine mascate** in secventa ***N – C* - 2 – *C* - 3**
- foarte reactivi la ***C* – 3**
- foarte reactivi si, ca atare, **neselectivi** in **mediu puternic** acid (**nitrare si sulfonare**)
- unii **derivati deja substituiti la *C* – 3** manifesta **inca electrofilicitate** (comportare cu **mare valoare sintetica**)
- **reactivitatea inelului pirolic** o **depaseste net** pe cea a **inelului benzenic**

a) Reactia Mannich si functionalizarea mai departe:



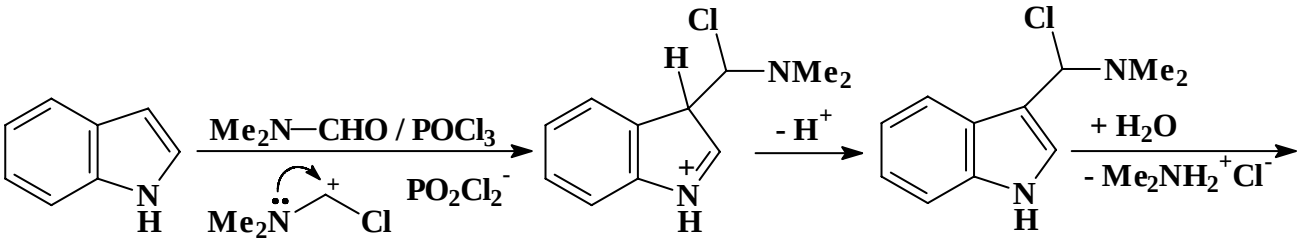
- **alta posibilitate de a genera carbocationi stabilizati la *C* - 3:**

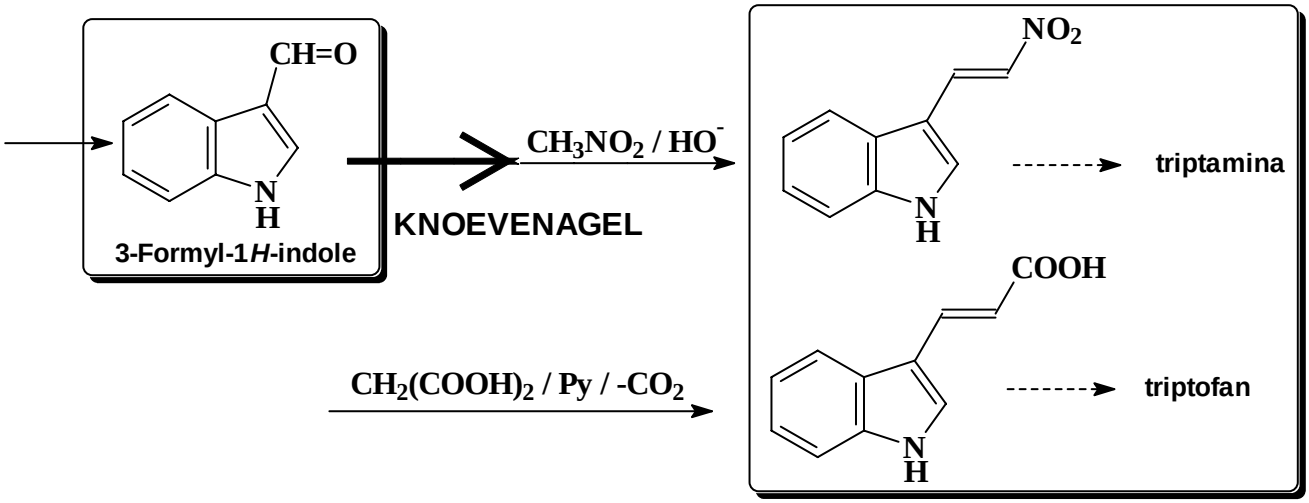




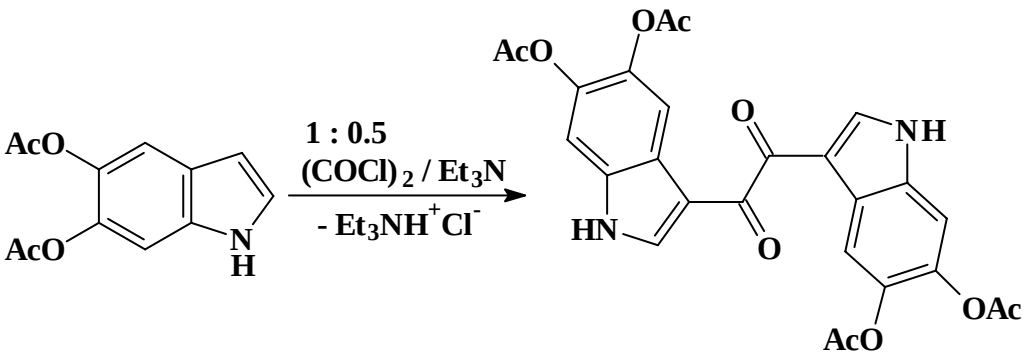
b) Reactia Vilsmeier si aplicatii:

- are loc in conditii **similare formilarii pirolului:**



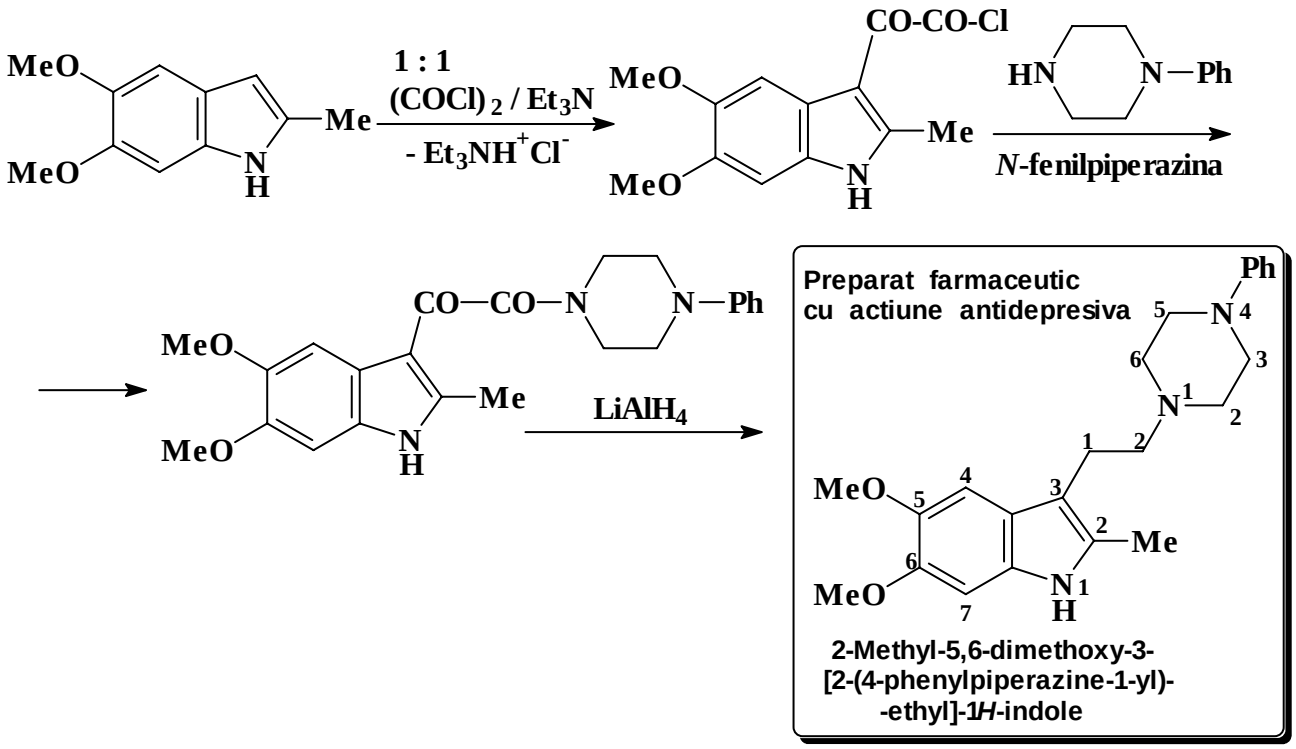


c) *C* - acilarea la *C*-3: se realizeaza **fara catalizator, foarte regioselectiv,** pe **forma neutra a indolului, direct cu cloruri acide** si in **tampon bazic**



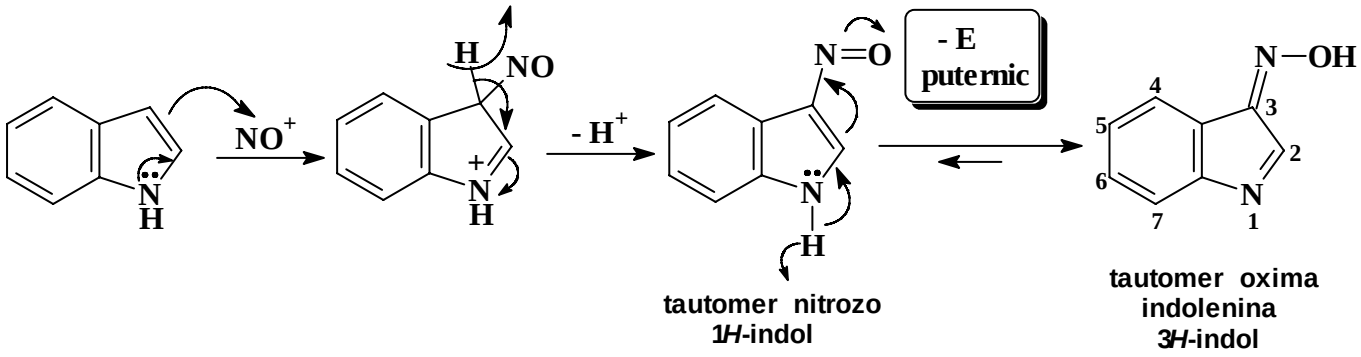
- reactia are loc in conditii **extrem de blande**; se poate opri la stadiul de **monoclorura acida** (intermediara) sau **structuri dimerice**, ca mai sus; se aplica in **sinteza farmaceutica**.

- **exemplu de acilare mixta, nesimetrica:**



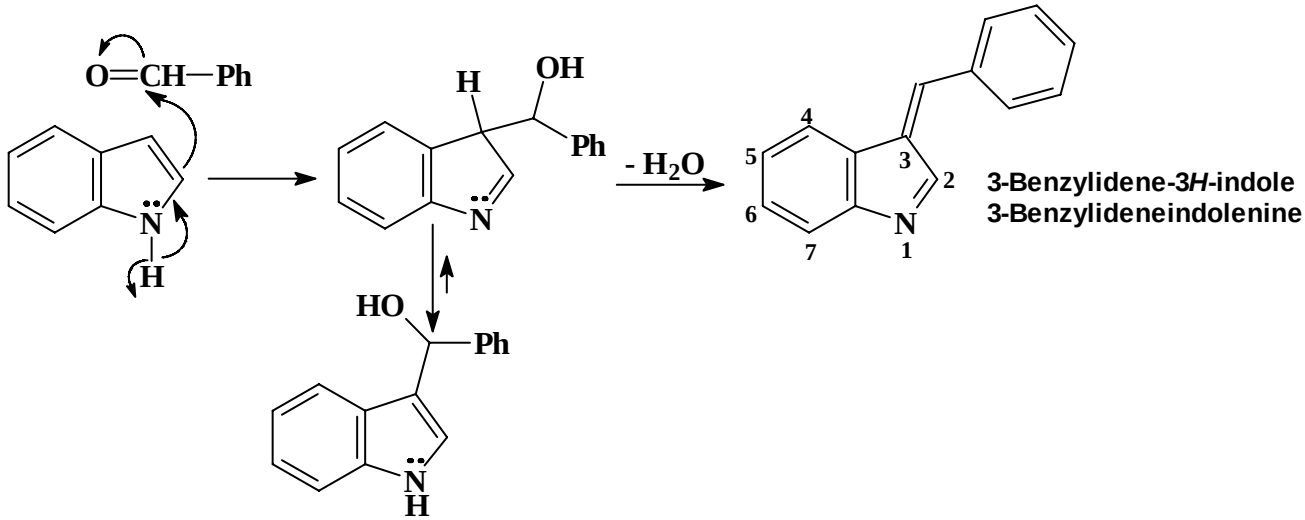
d) reactii SE la *C* – 3 cu stabilizarea formei 3*H* indolice:

Exemplul 1: nitrozarea

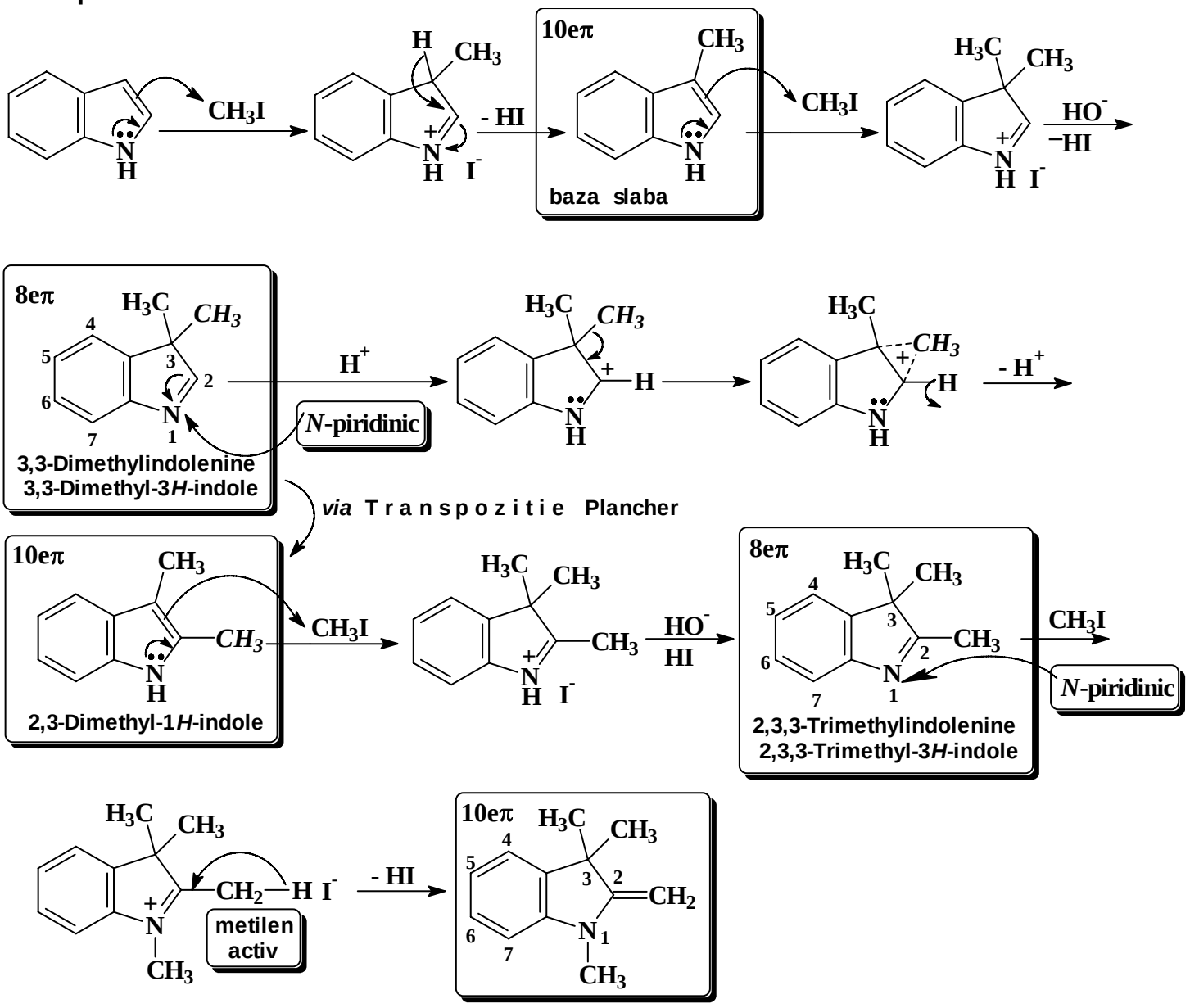


- **tautomerul oxima** (indoleninic) este **mai stabil**: contine perechea de centre **acid** si **baza slabe** (**=N-OH** respectiv **-N=**) si prezinta o conjugare mai extinsa (11 fata de 9 centre)

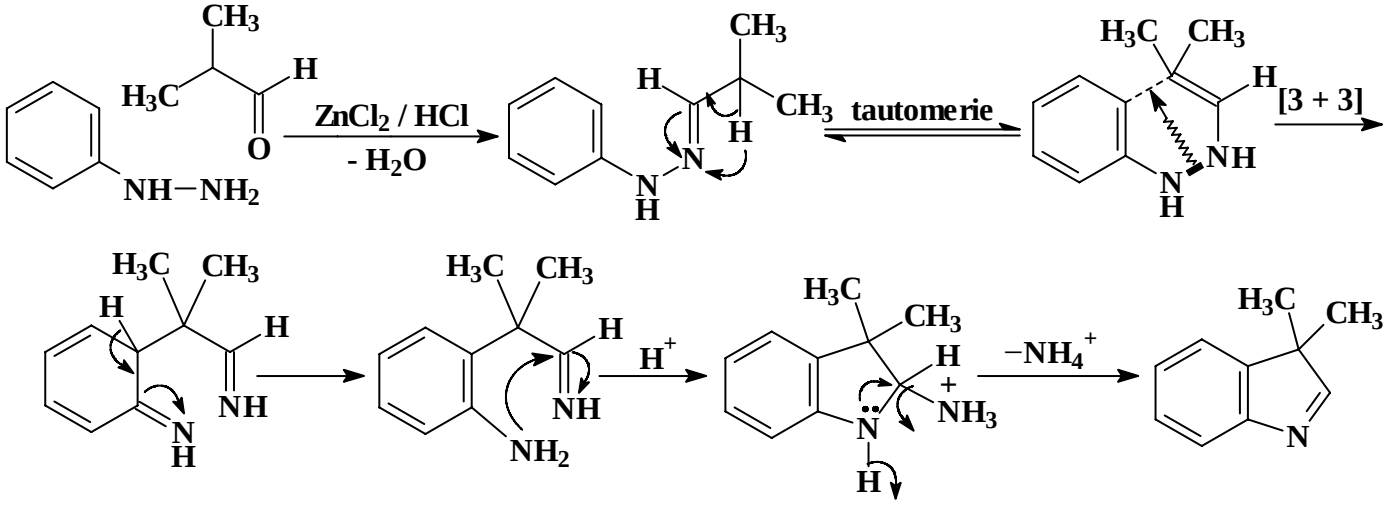
Exemplul 2: reactia cu aldehide aromatice



Exemplul 3: metilarea la *C* – 3



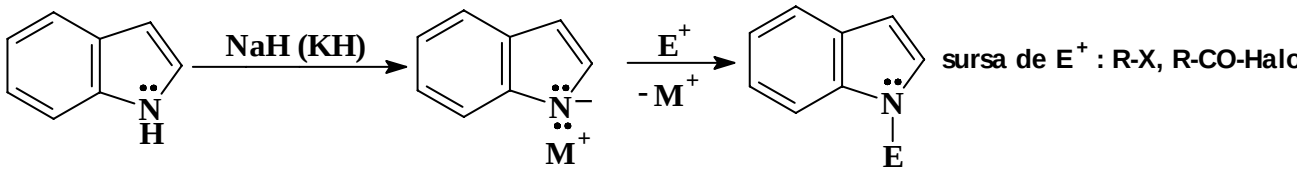
Nota 1: regioselectivitatea la ***C* - 3** metilarii este data de efectul de orientare al grupei **NH**
Nota 2: pe masura ca **metilarea avanseaza**, **bazicitatea** in partea **heterociclica creste**
Nota 3: **transpozitia Plancher** pune in evidenta, indirect, **stabilitatea mai mare** a formei **1*H*-indolice** ***vs.*** **3*H*-indolice (indoleninice, de-asemenea accesibila in varianta *Fischer*)**



3.2. Functionalizarea prin SE *via* metalare:

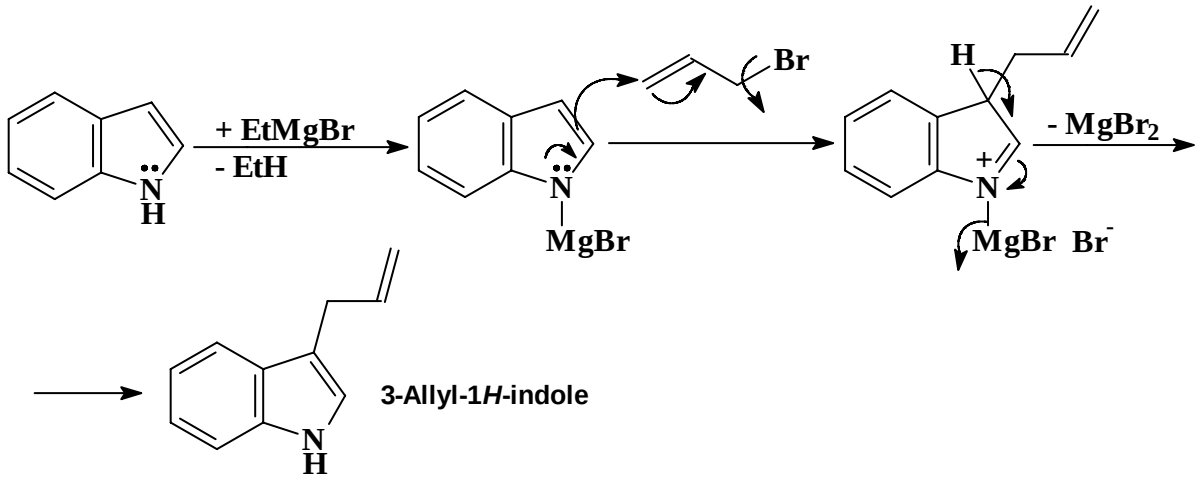
- asemanatoare pirolului
- deprotonarea la **N*H*** (pKa cca. 17) furnizeaza o baza puternica
- **nucleofilicitatea** anionului depinde de **electropozitivitatea** metalului

Exemplul 1: metale puternic alcaline → ***N* - substitutie**

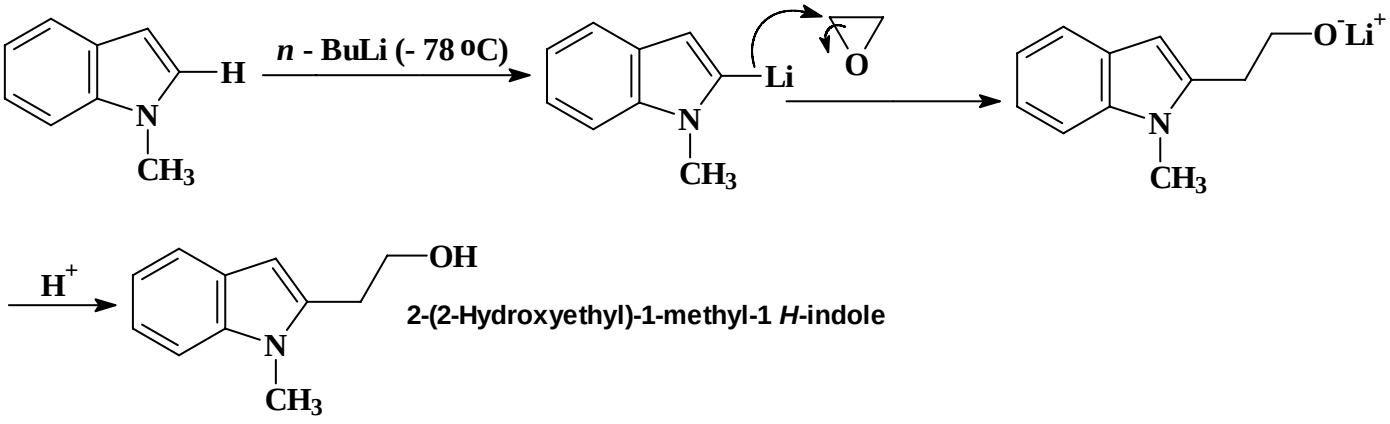


Nota: utilizarea ***n* - BuLi** pentru deprotonarea la N***H*** **nu da** rezultate **reproductibile**

Exemplul 2: in cazul utilizarii **reactivilor Grignard**, orientarea **SE** este la ***C* – 3**



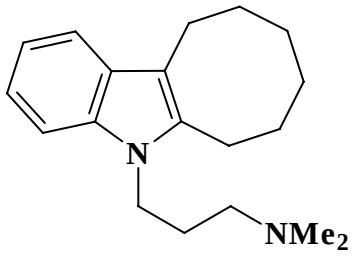
Exemplul 3: utilizarea ***n* - BuLi** este eficienta asupra ***N* – metilindolilor** (ca forme ***N* – protejate**) si permite functionalizarea regioselectiva la ***C* - 2** ***via*** ***C* – 2** litioderivati



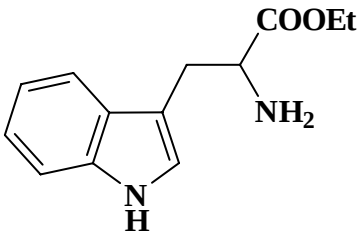
Nota: este metoda predilecta de completare a functionalizarii la ***C* - 3**

P – 5

P-5.1. Indicati o metoda de obtinere a compusului indolic de mai jos, preparat farmaceutic cu actiune antidepresiva:



P-5.2. Indicati o metoda de preparare a compusului indolic de mai jos pornind, ca materii prime de baza, de la indol ca atare si nitroacetat de etil:



P-5.3. Explicati comportarea indolului *N*-substituit de mai jos in reactia de metalare cu *n*-BuLi.