Nomenclatura degli eterocicli secondo Hantzsch-Widmann

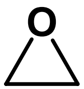
Eteroatomo	Prefisso	Prefisso in inglese
O	ossa	oxa
S	tia	thia
N	aza	aza
P	fosfa	phospha
Si	sila	sila

http://www.acdlabs.com/iupac/nomenclature

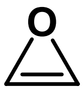
Nomenclatura degli anelli

Dimensione	Insaturi	Saturi	Saturi contenenti azoto
3	irene	irano	azirina
4	ete	etano	azetidina
5	olo	olano	azolidina
6	ina	ano	-
7	epina	epano	-

Esempi

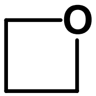


ossirano

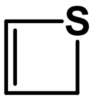


ossirene

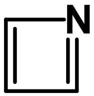
azirina



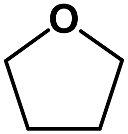
ossetano



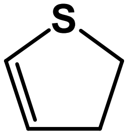
tietene



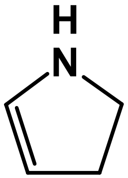
azete



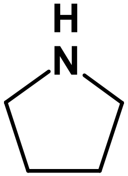
ossolano



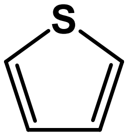
tiolene



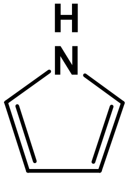
azolina
pirrolidina



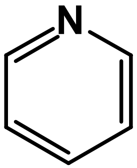
azolidina
pirrolidina



tiolo
tiofene



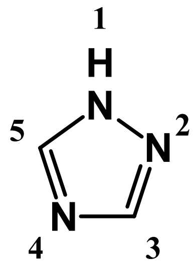
azolo
pirrolo



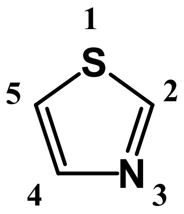
azina
piridina

Numerazione degli anelli con più eteroatomi

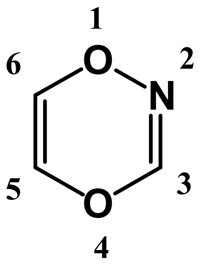
Sequenza di priorità: ***O*** **precede** ***S*** **precede** ***N***



1,2,4-triazolo
(*non* 1,3,5-triazolo)

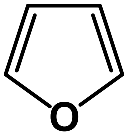


1,3-tiazolo
(*non* 1,3-azatiolo)

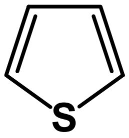


1,4,2-diossazina

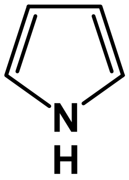
Alcuni nomi comuni



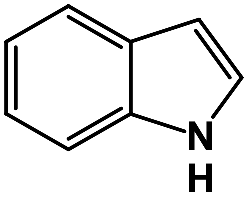
furano



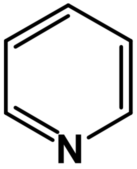
tiofene



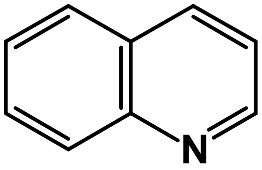
pirrolo



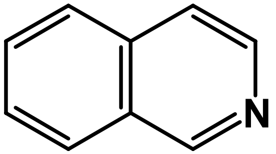
indolo



piridina

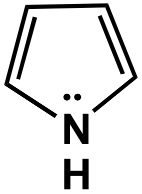


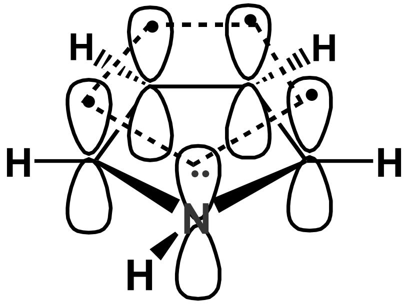
chinolina



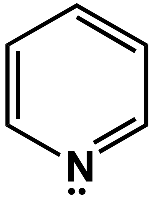
isochinolina

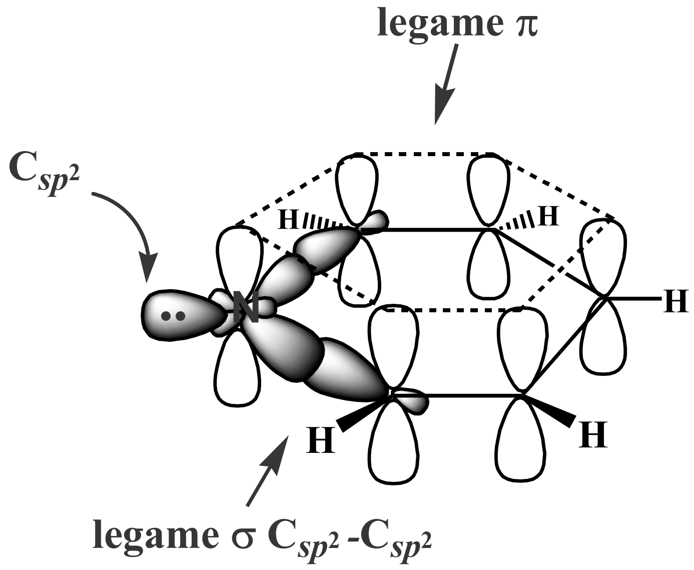
Pirrolo: un eterociclo elettron-ricco





Piridina: un eterociclo elettron-povero





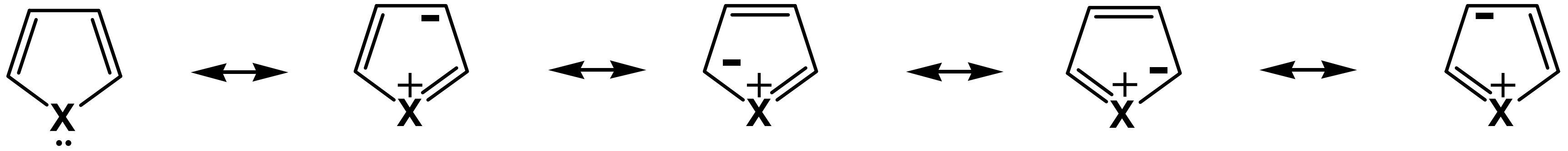
Indici di aromaticità

(C.W. Bird, Tetrahedron 1992, 48, 335)

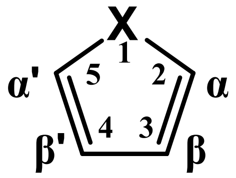
Benzene	**100**	**Naftalene**	**142**
Furano	**53**	**Indolo**	**146**
Tiofene	**82**	**Chinolina**	**134**
Pirrolo	**85**		
Piridina	**86**		

Furano - Tiofene - Pirrolo

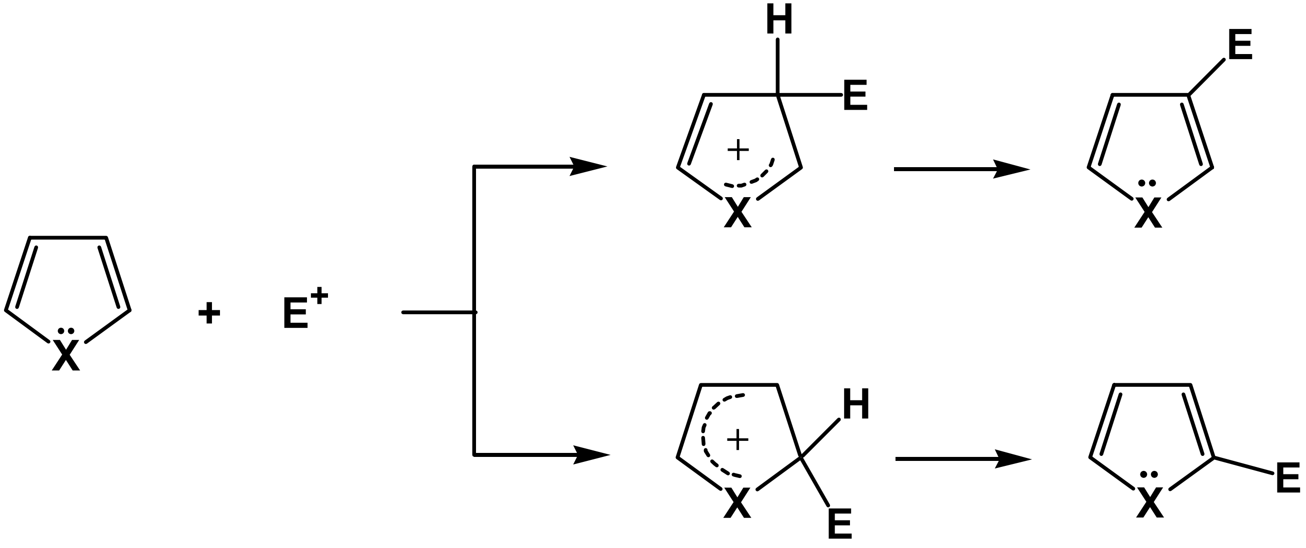
X = *O, S, NH*



Sostituzione elettrofila



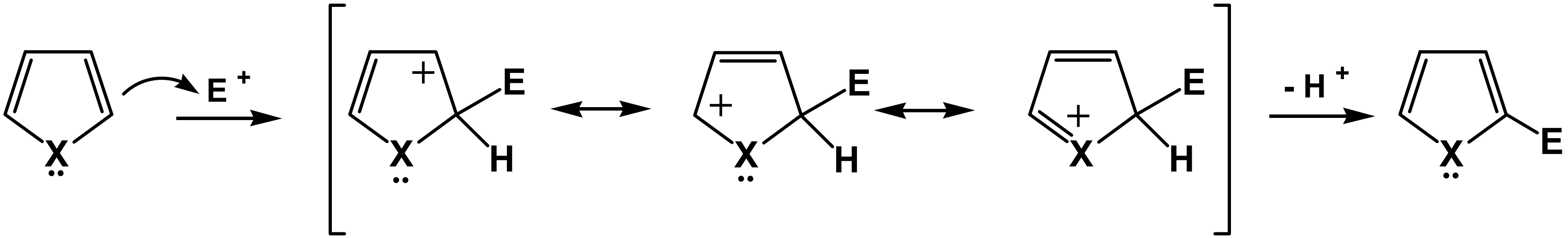
X = *O, S, NH*

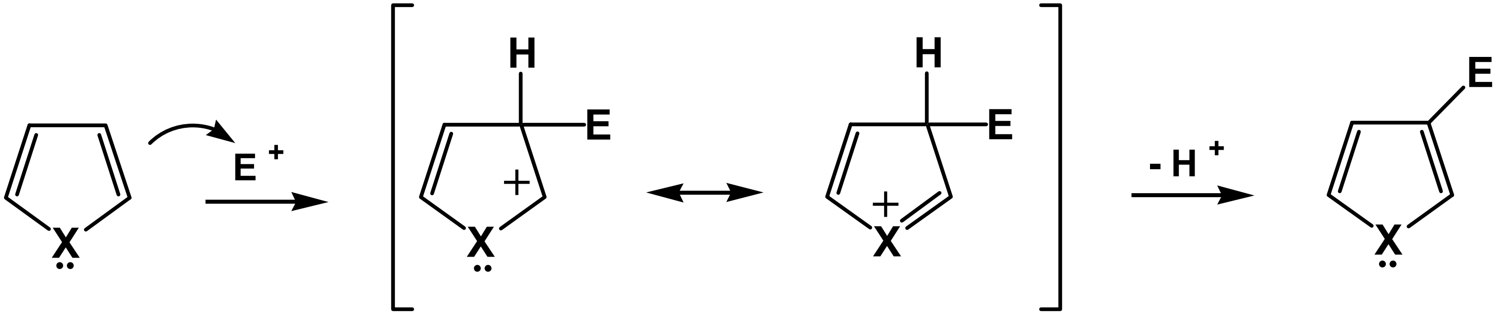


Furano - Tiofene - Pirrolo

La sostituzione elettrofila in α *è favorita*

X = *NH, S, O*





Confronti di aromaticità tra Furano, Tiofene, Pirrolo

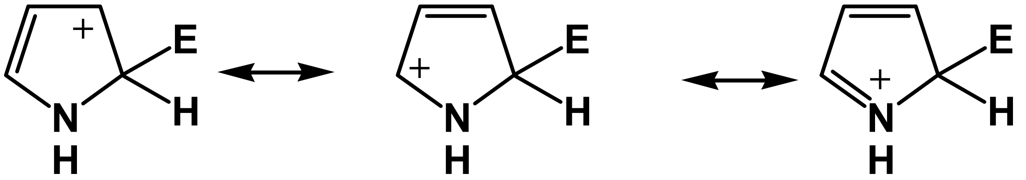
	Furano	Tiofene	Pirrolo
Energia di risonanza (Kcal/mole)	**16**	**34**	**25**

Tiofene > Pirrolo > Furano

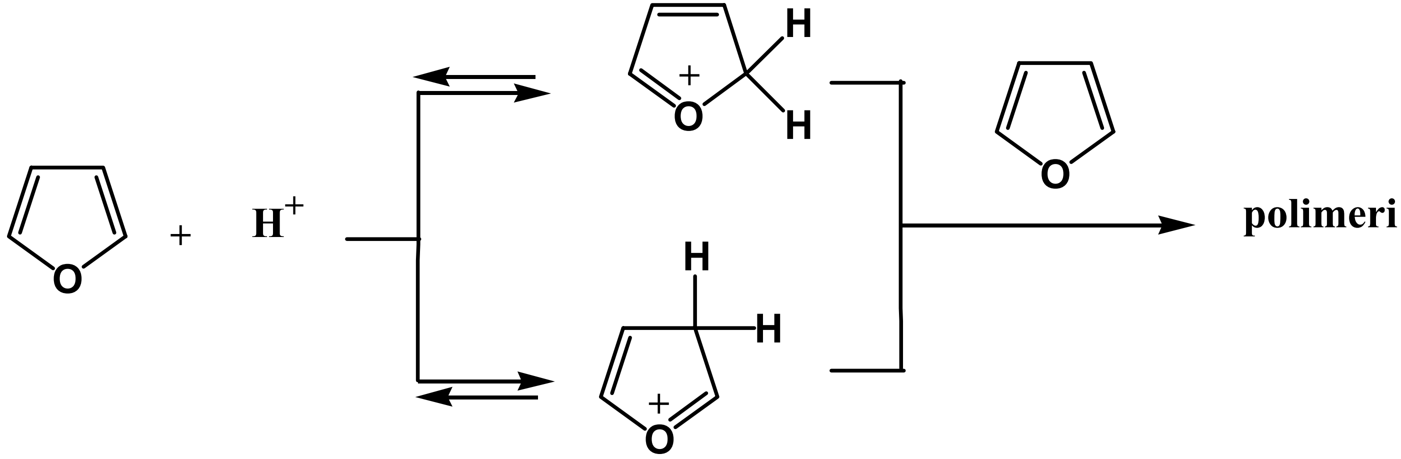
Confronto di reattività tra Furano, Tiofene, Pirrolo

	Furano	**Tiofene**	**Pirrolo**
Reattività in confronto al benzene	**10^{11}**	**10^{3}**	**10^{15}**

- **la maggiore stabilizzazione dell'intermedio tramite la struttura imminio spiega la maggiore reattività del pirrolo nonostante che la sua aromaticità sia superiore a quella del furano.**



Le reazioni di protonazione di furano, tiofene, pirrolo e i loro effetti



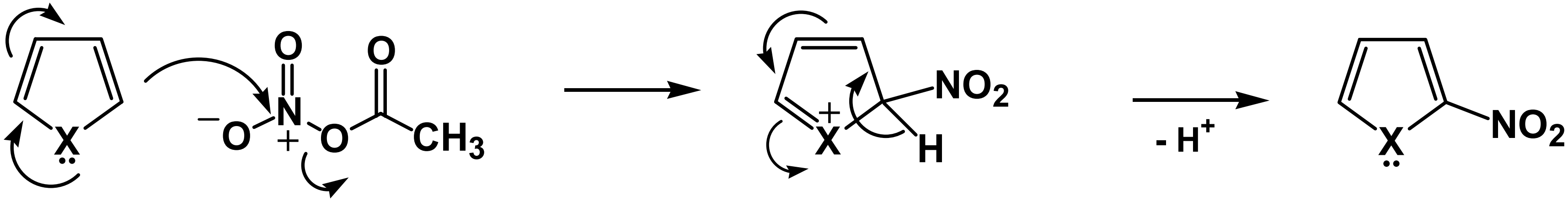
- il pirrolo si comporta analogamente
  - il tiofene è stabile agli acidi

Nitrazione e solfonazione

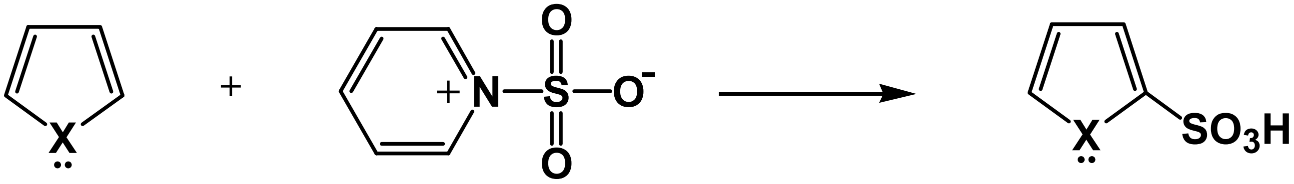
X = NH, S, O

Agente nitrante: **nitrato di acetile (anidride mista)**

$$HNO_3 + (CH_3CO)_2O \rightleftharpoons CH_3COONO_2 + CH_3COOH$$

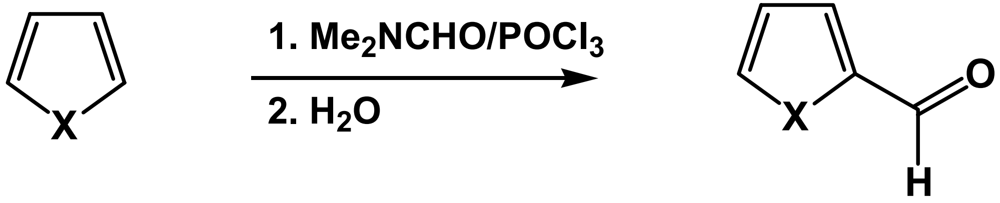


Agente solfonante: **Py·SO$_3$**

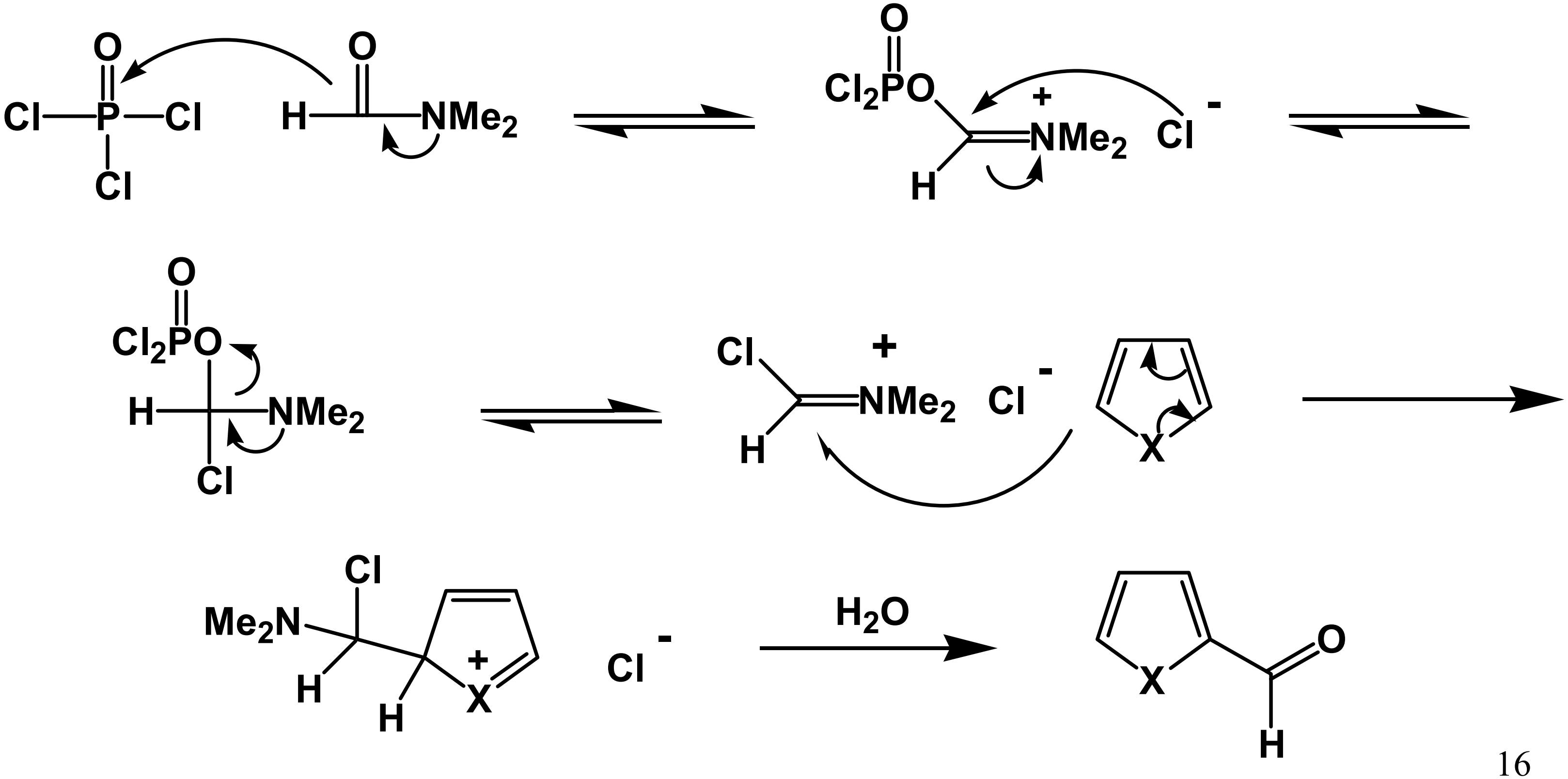


Altri esempi di sostituzioni elettrofile

- **formilazione di Vilsmeier**

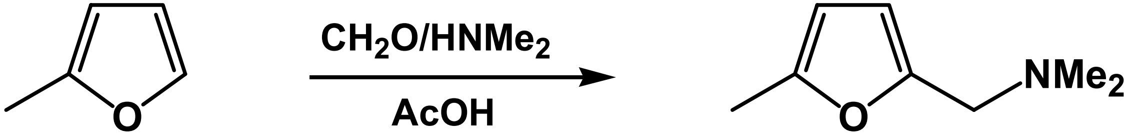


X = NH, S, O

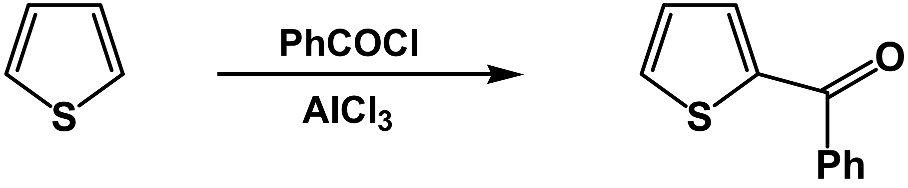


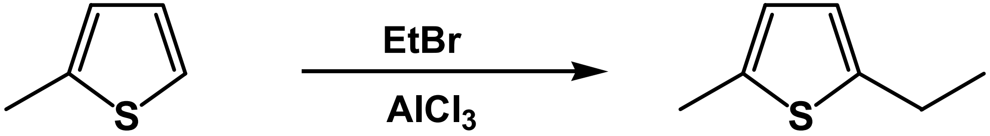
Altri esempi di sostituzioni elettrofile

- **reazione di Mannich**

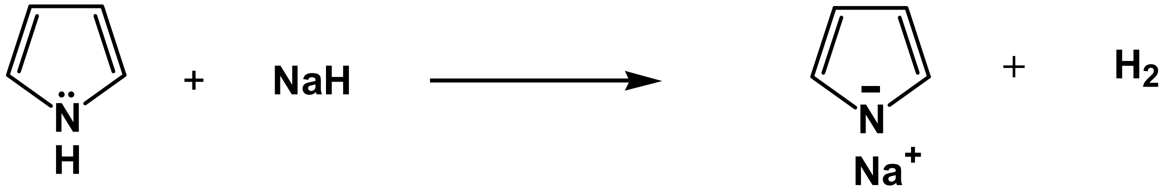


- **alchilazione e acilazione *(soltanto su tiofene*)**

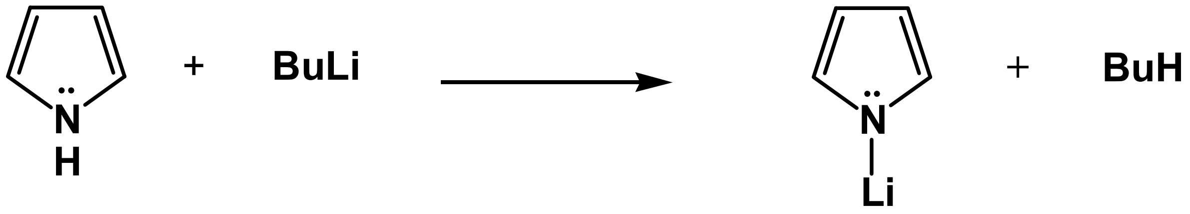


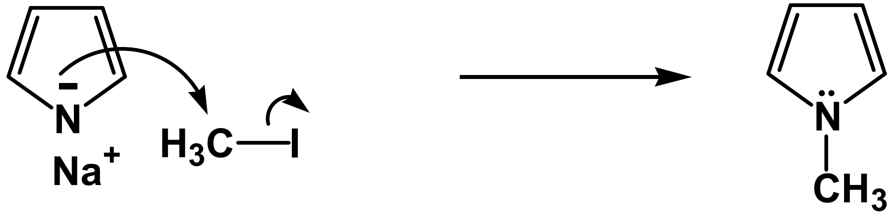


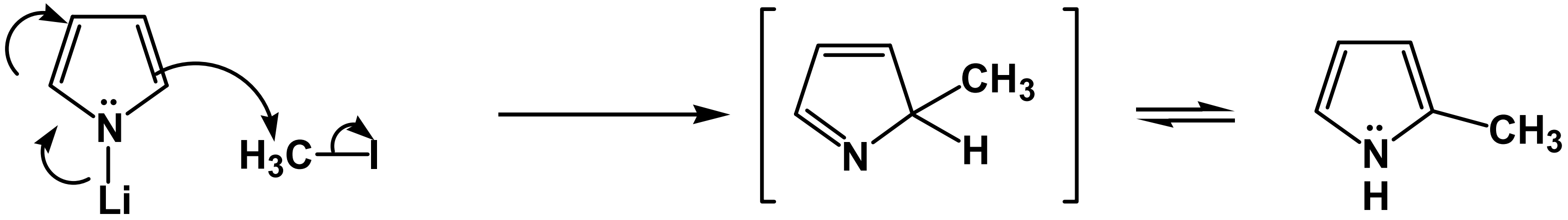
Reazioni del pirrolo con basi: reazione di alchilazione



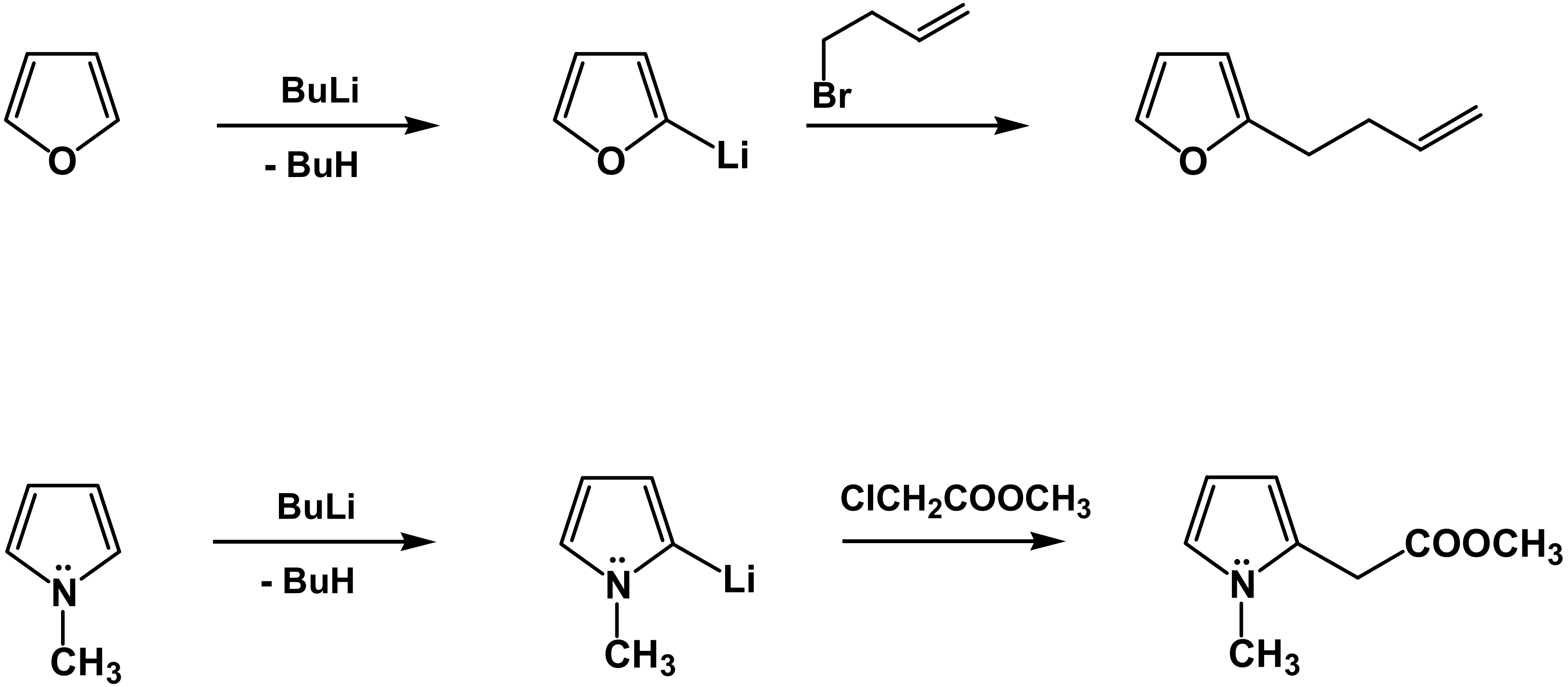
$\boxed{pK_a = 17.5}$





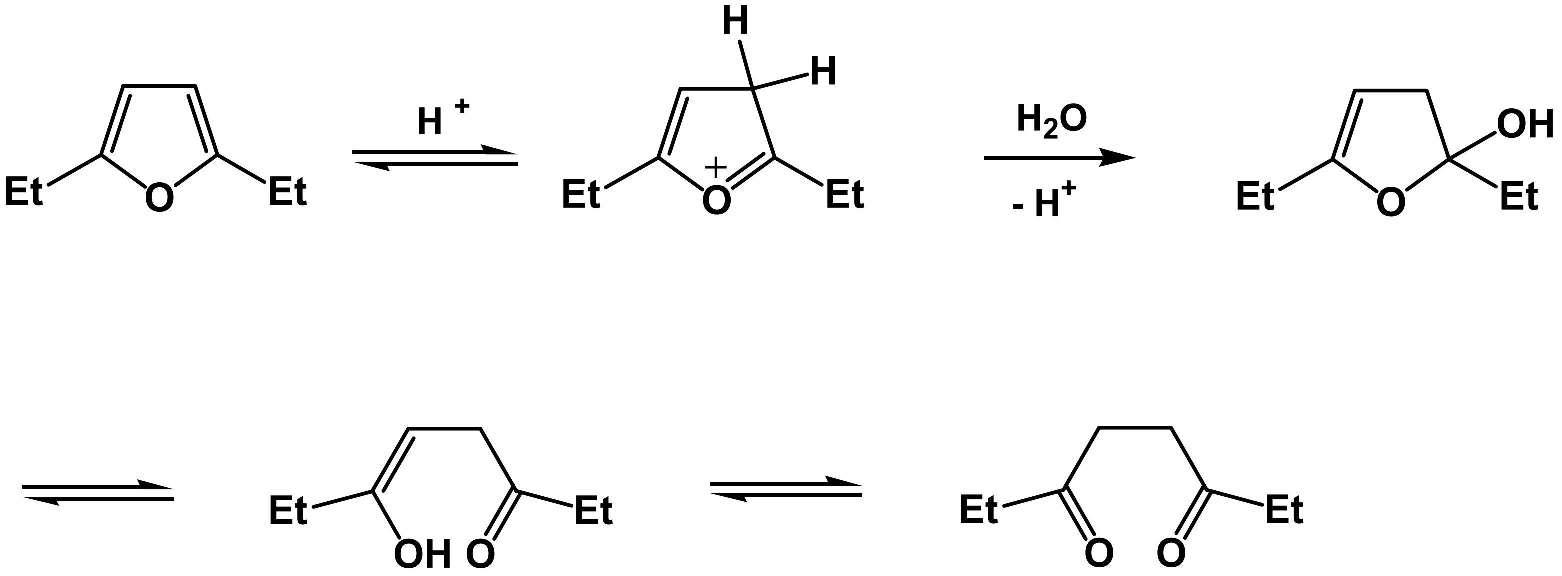


Litiazione di Furano - Tiofene - Pirrolo

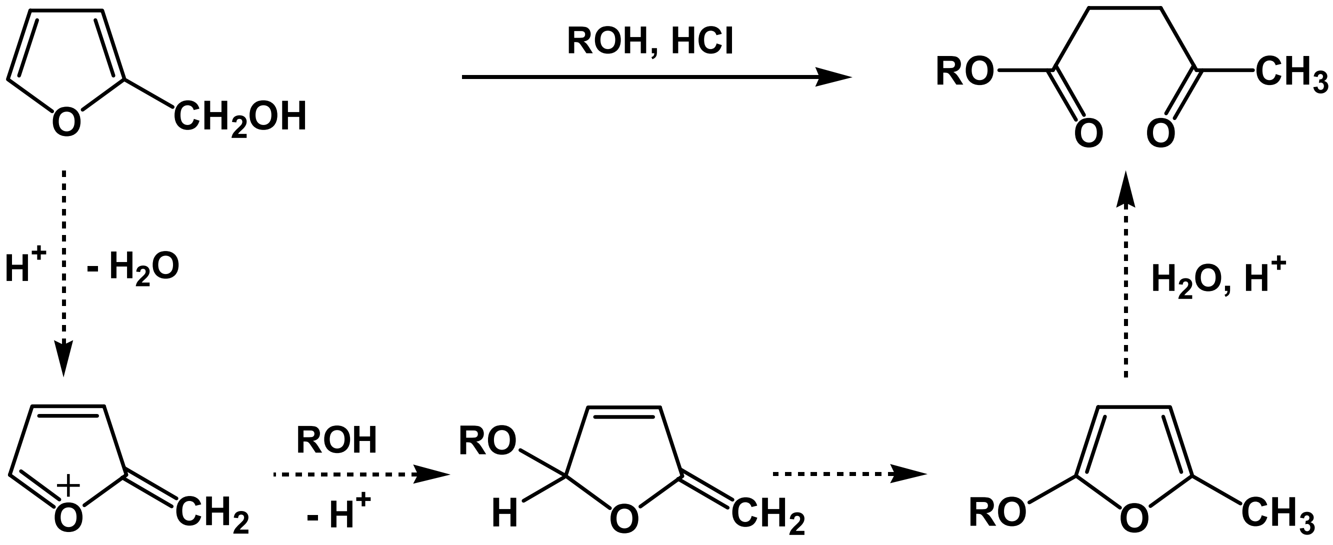


Gli eterocicli come intermedi nella sintesi organica

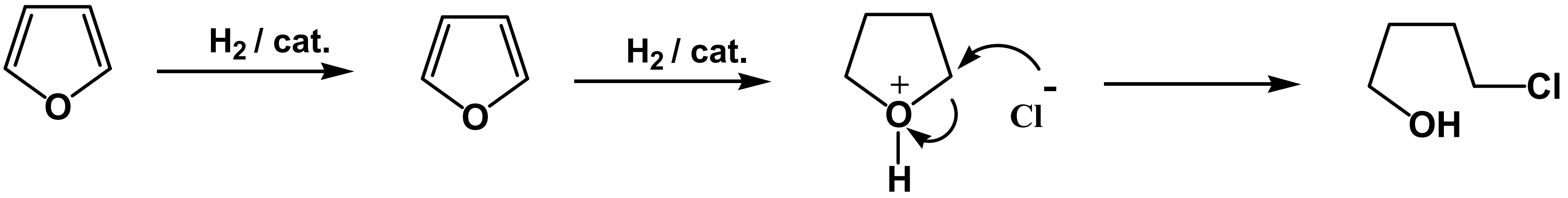
Furano ⟶ **Composti γ-dicarbonilici**



Esercizio 1.

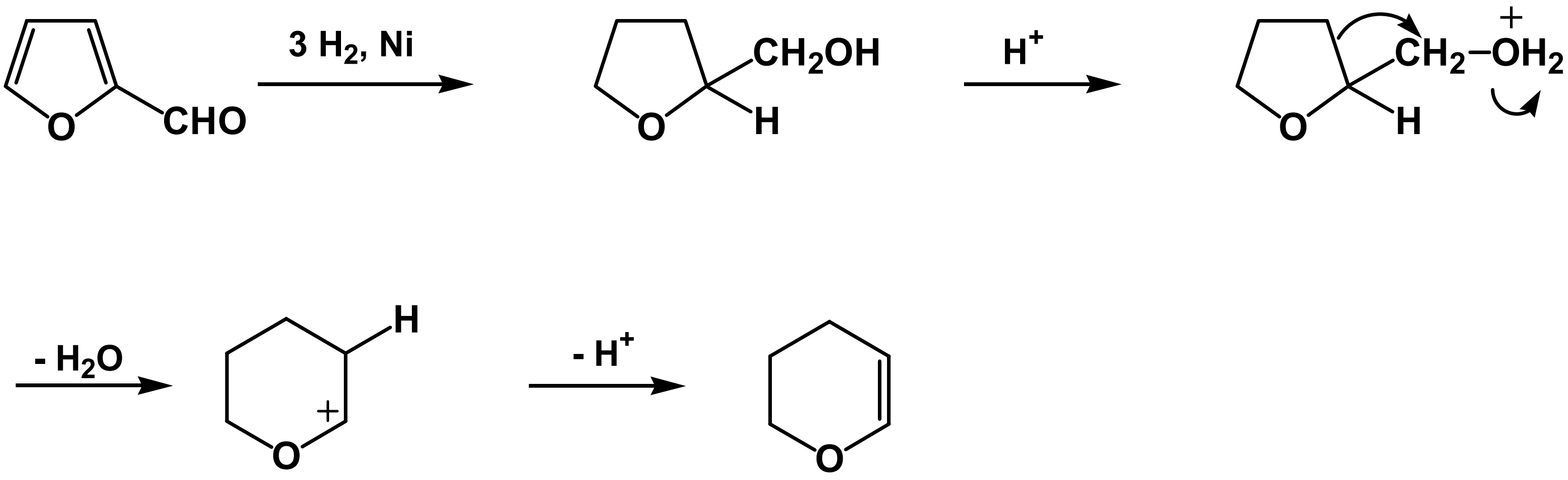


Esercizio 2.



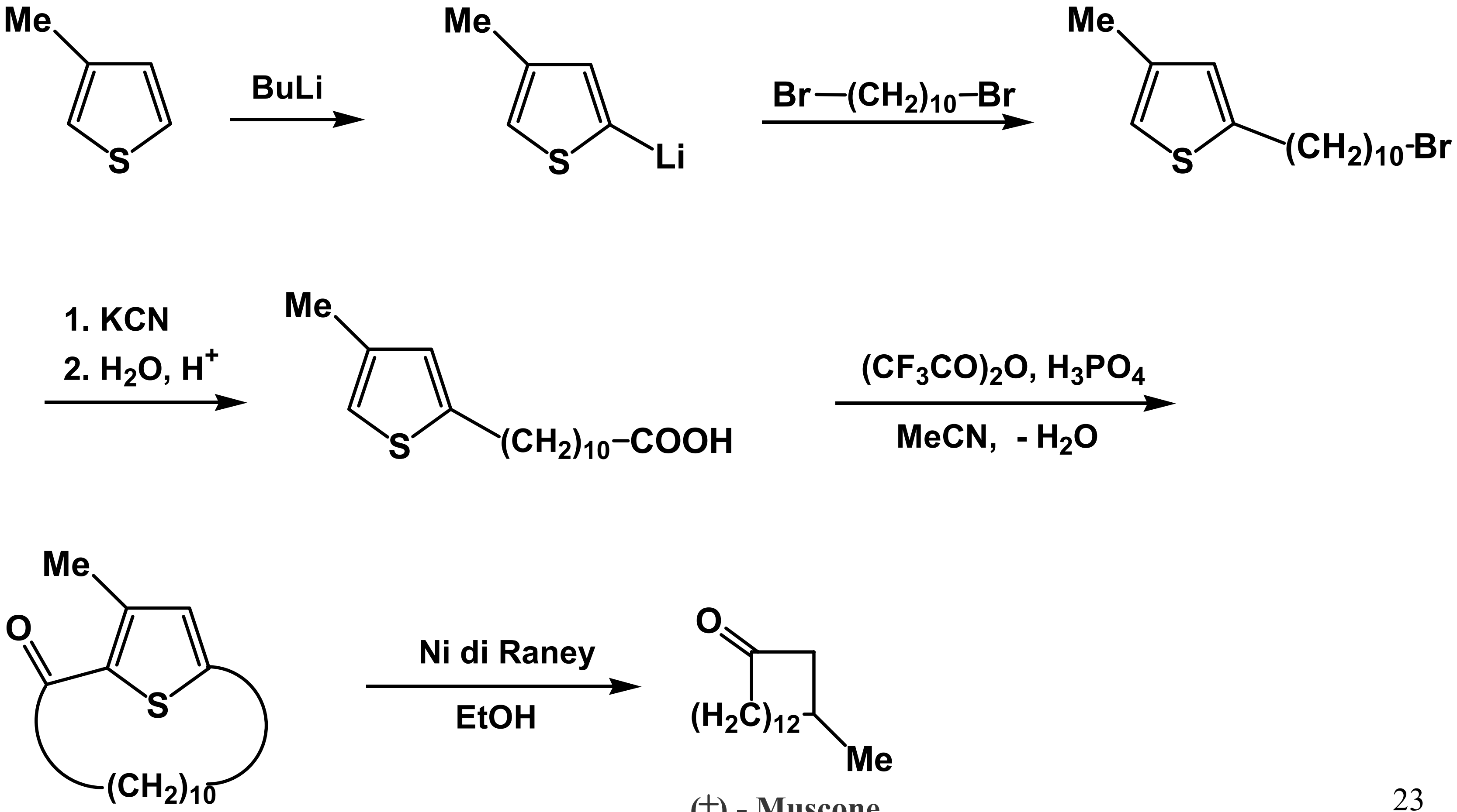
Gli eterocicli come intermedi di sintesi organica

Alcol furfurilico ⟶ **diidropirano**



Gli eterocicli come intermedi di sintesi organica

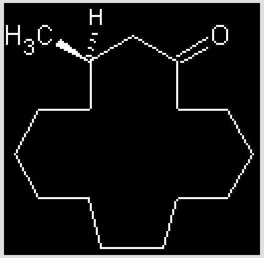
3-Metiltiofene ⟶ **(±)- Muscone**

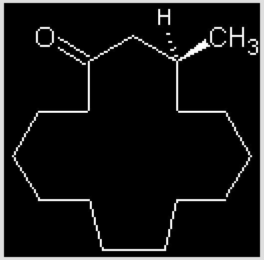


(±) - Muscone

(R)-(-)-muscone [(3R)-(-)-3-metilciclopentadecanone] - descritto dai profumieri come "profumo di muschio ricco e potente"
Soglia olfattiva = 61 ppb

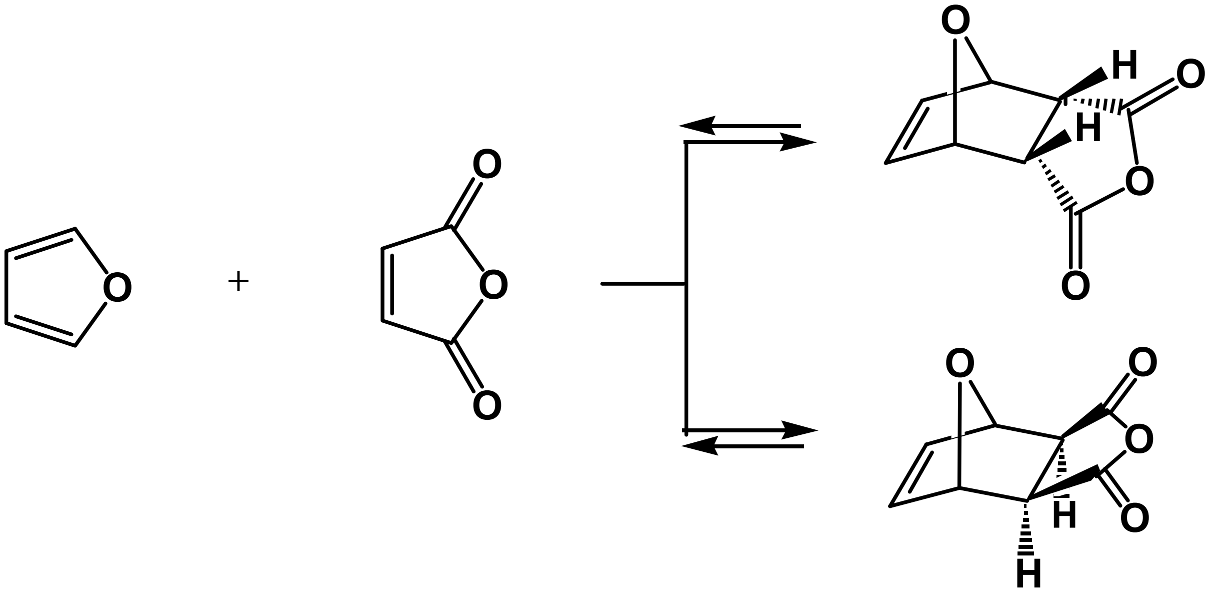
(S)-(+)-muscone [(3S)-(+)-3-metilciclopentadecanone] - descritto dai profumieri come "profumo di muschio scadente e debole"
Soglia olfattiva = 223 ppb





Lo zibetto (dall'arabo zabad) è un piccolo felino africano. L'assoluto di zibetto è ricavato purificando la secrezione peri-anale dell'animale in alcool. Lo zibetto strofina il suo posteriore sui tronchi e sulle rocce per segnalare la sua presenza ai rivali e alle femmine.

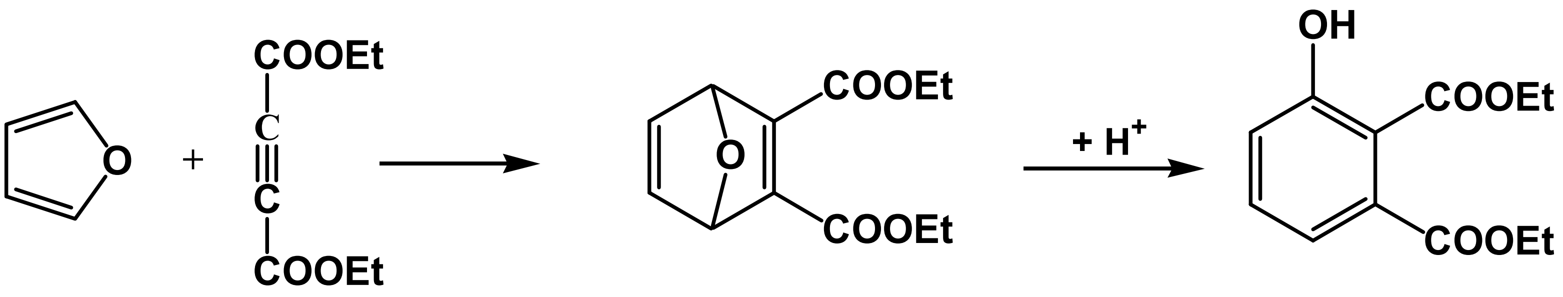
La reazione di Diels-Alder sul Furano

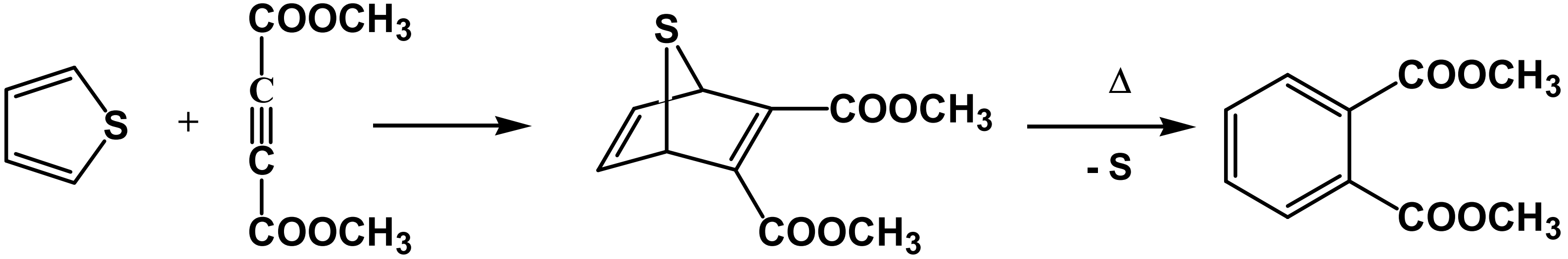


Addotto *endo*

Addotto *eso*

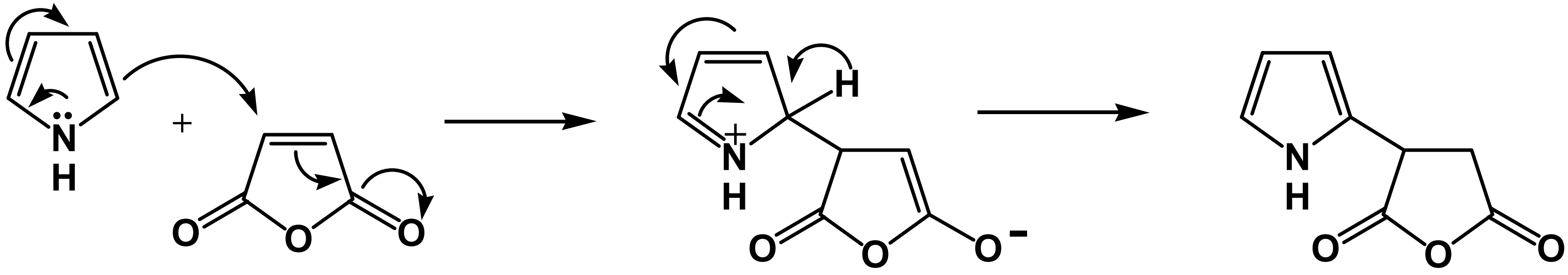
Il furano e il tiofene precursori di composti benzenici



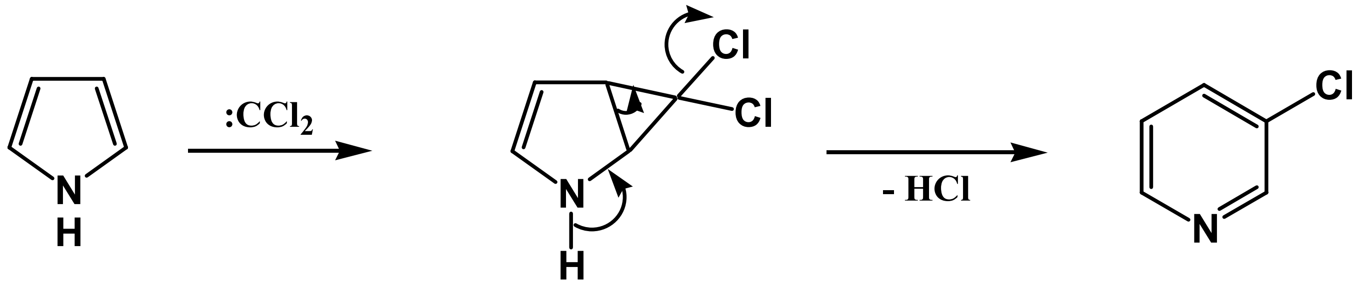


Esercizio:Il pirrolo non dà la reazione di Diels-Alder con l' anidride maleica.

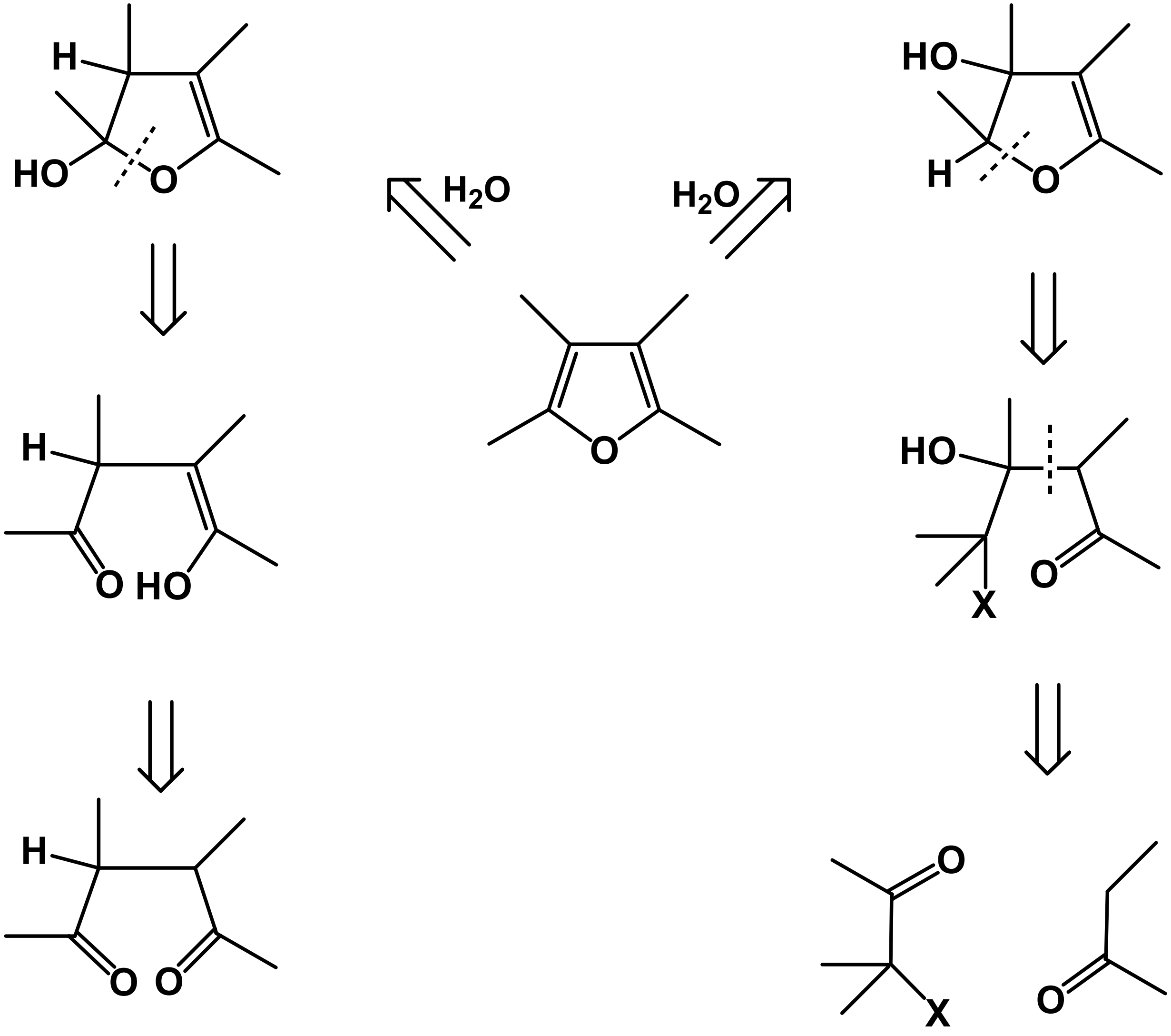
Si forma invece un prodotto di addizione di Michael. Quale sarà la struttura?



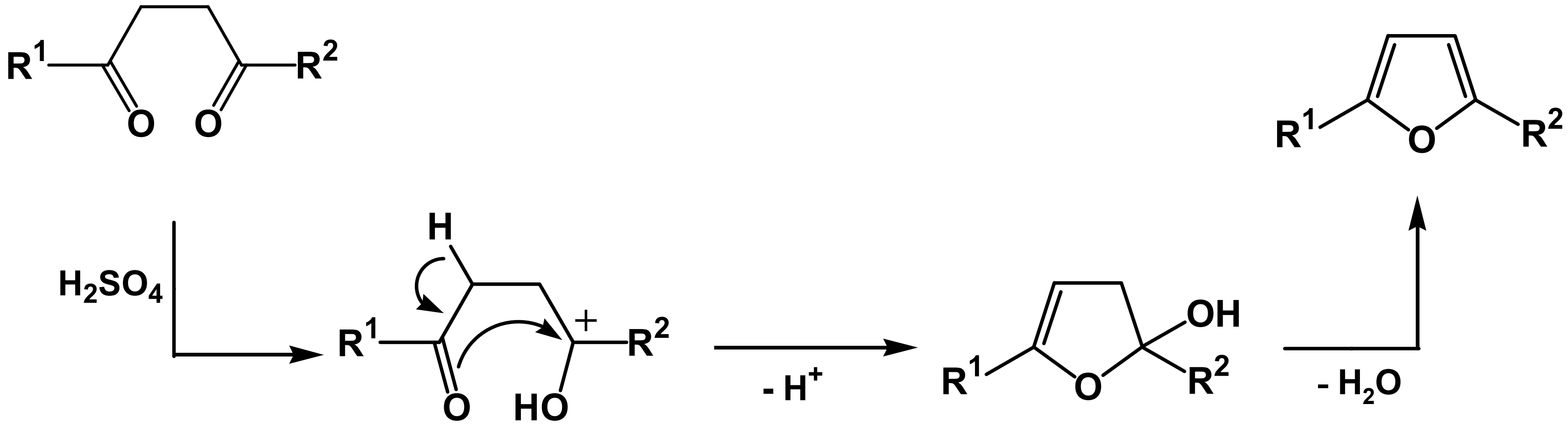
Esercizio: Il diclorocarbene (ottenibile da $CHCl_3$ e basi) reagisce con il pirrolo e dà un prodotto di cicloaddizione al doppio legame. Qual è la struttura di questo prodotto? Esso si trasforma facilmente per eliminazione di HCl in un derivato della piridina. Quale?



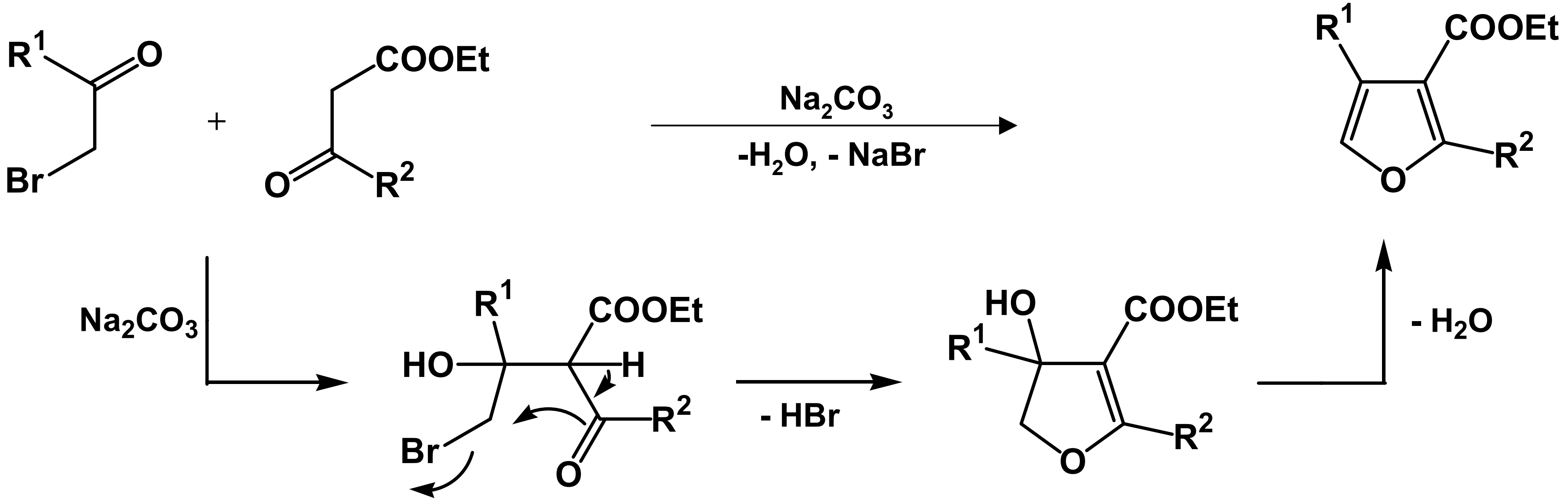
Retrosintesi del furano



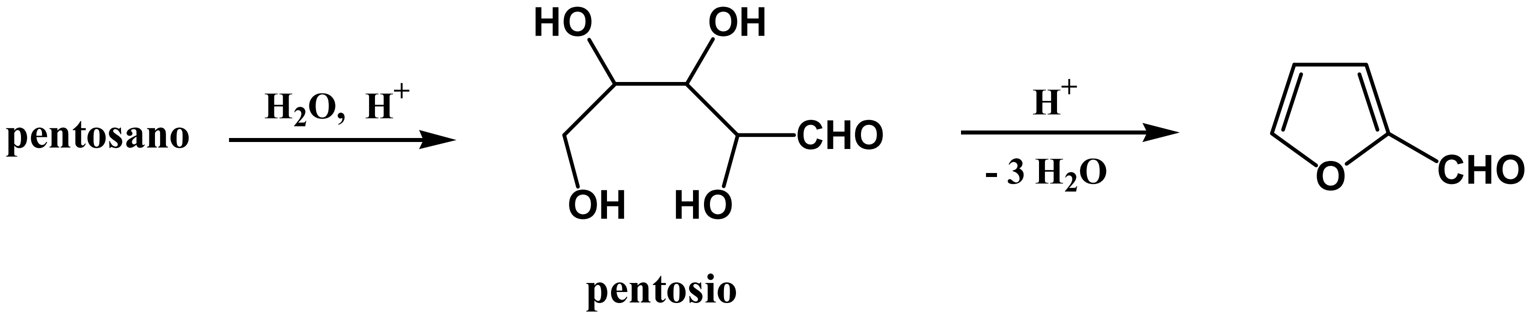
Sintesi del furano di Paal-Knorr



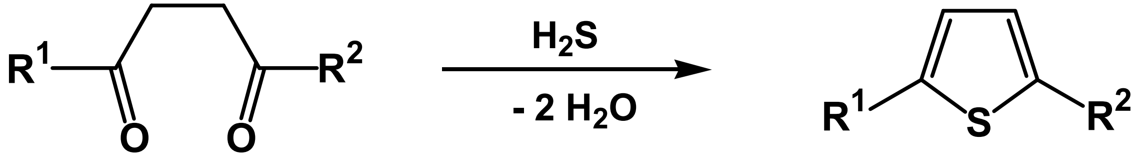
Sintesi del furano di Feist-Benary



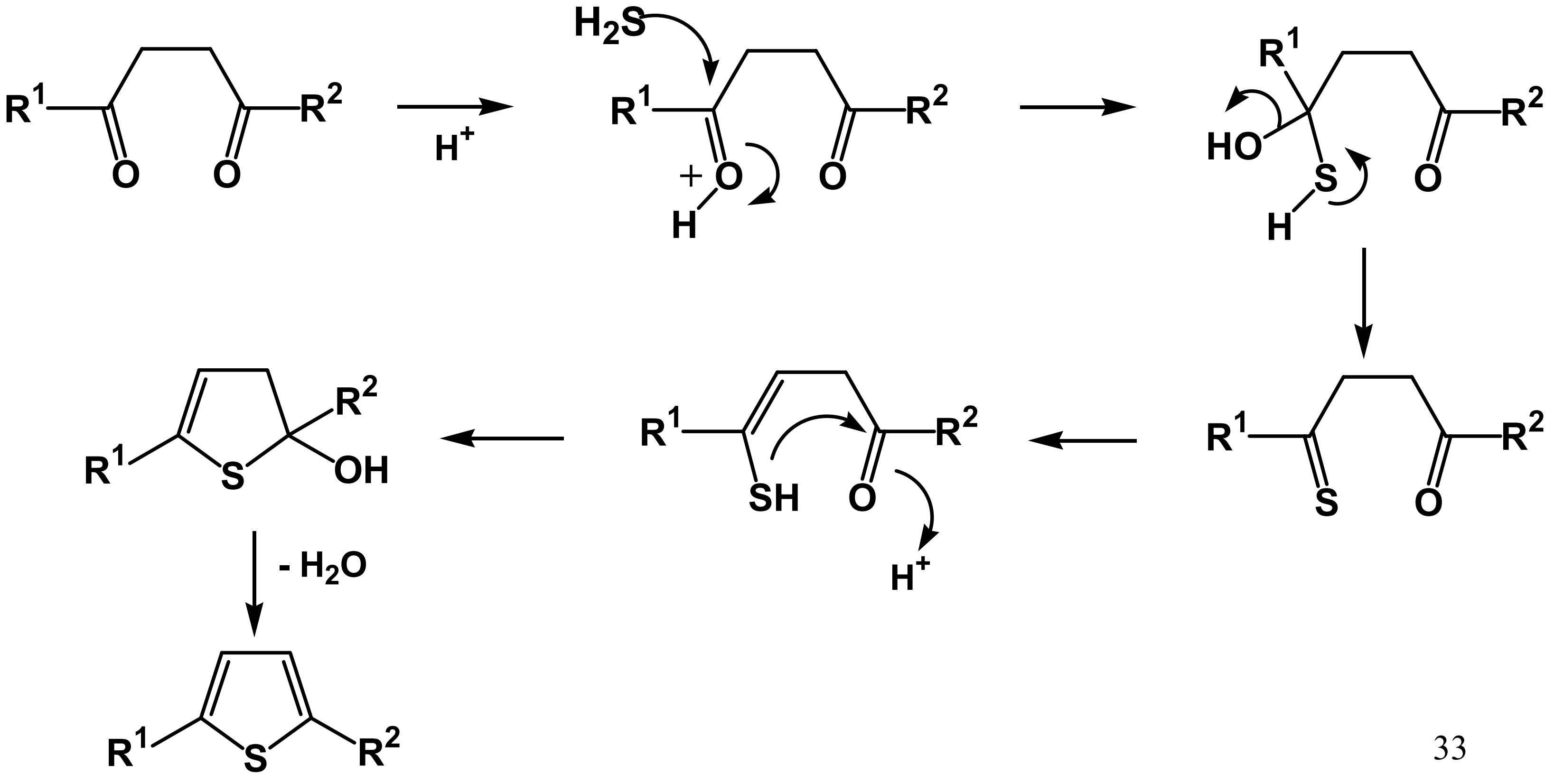
Sintesi del furfurale



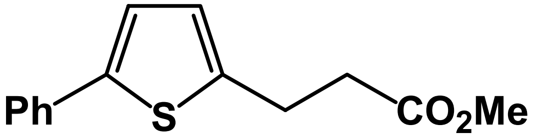
Sintesi del tiofene

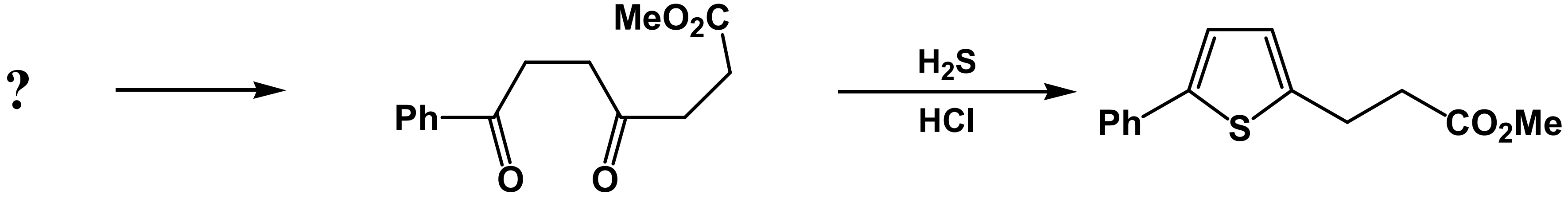


Meccanismo



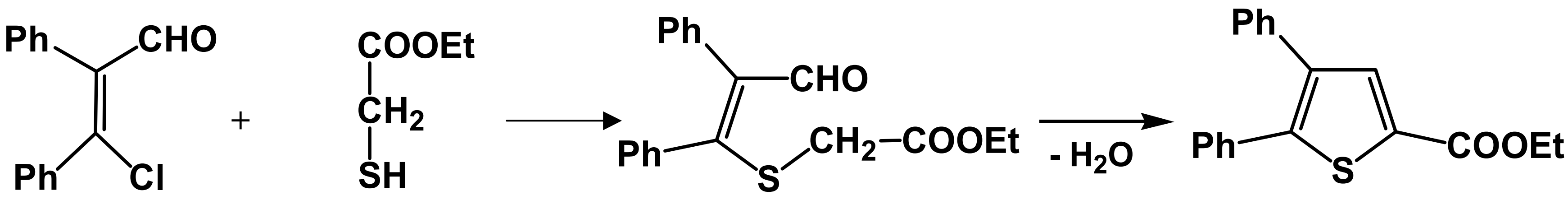
Esercizio: preparare



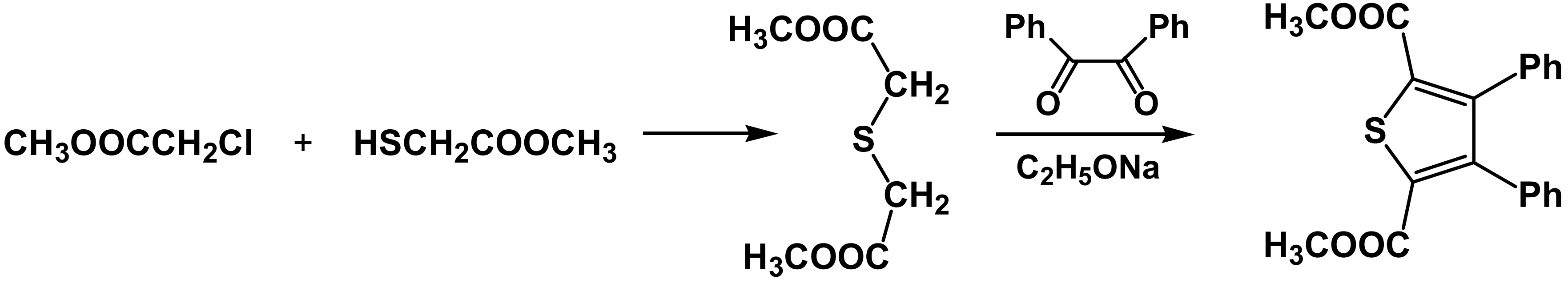


Sintesi del tiofene dall'acido tiolacetico

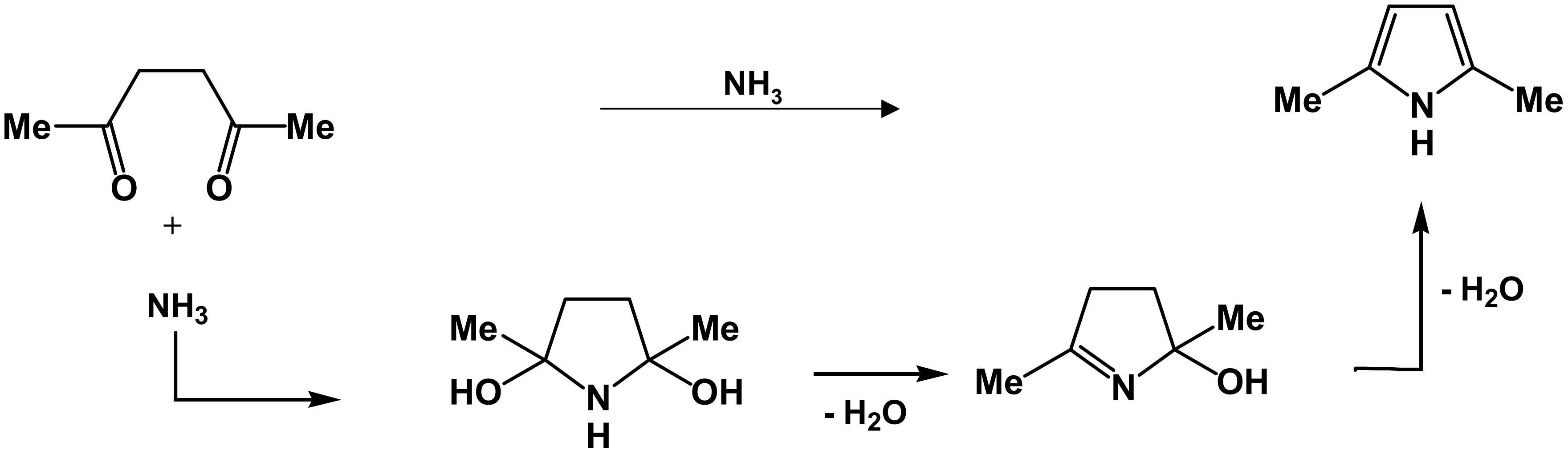
Sintesi di Fiesselmann



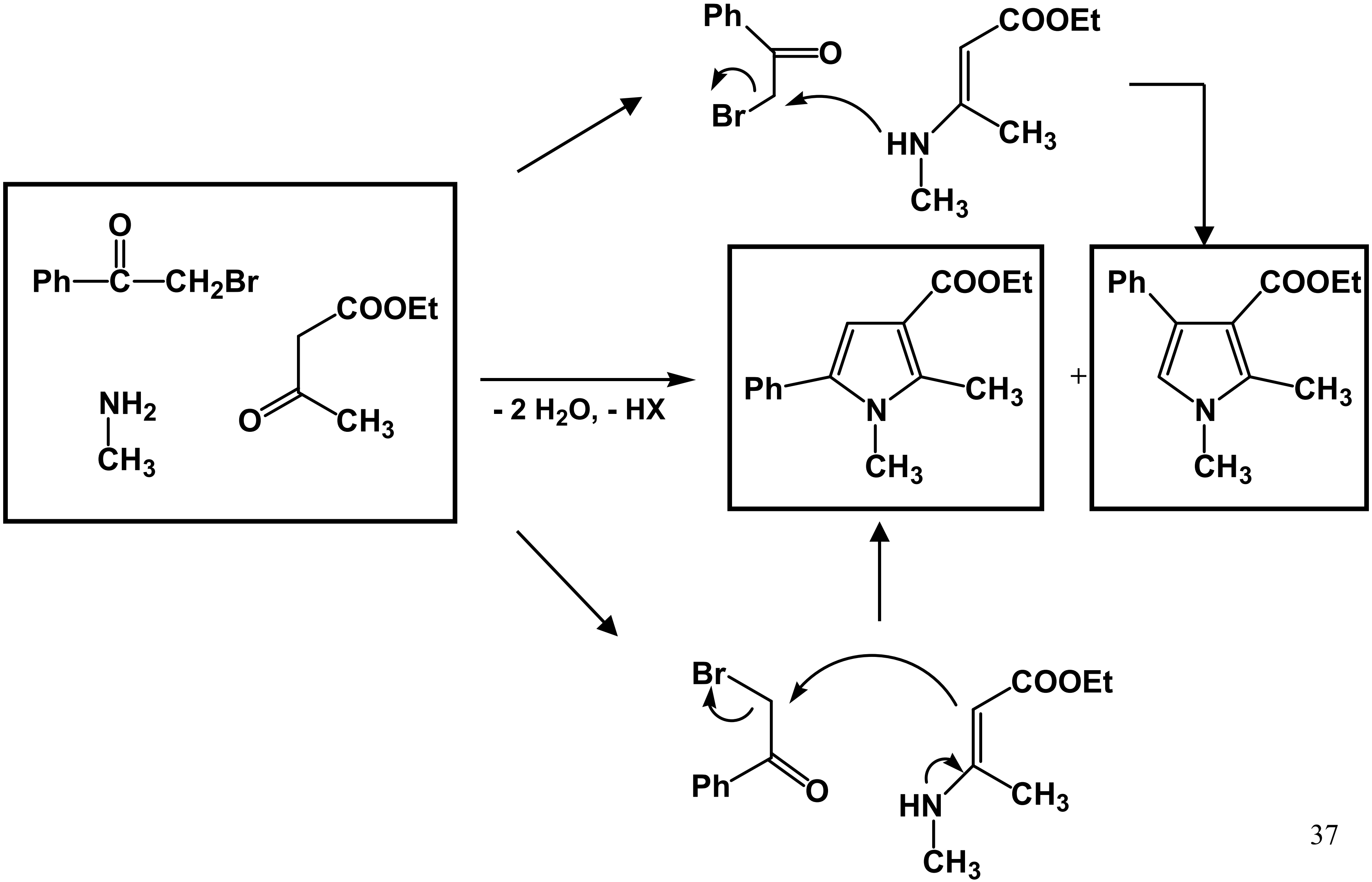
Sintesi di Hinsberg



Sintesi del pirrolo di Paal-Knorr



Sintesi del pirrolo di Hantzsch

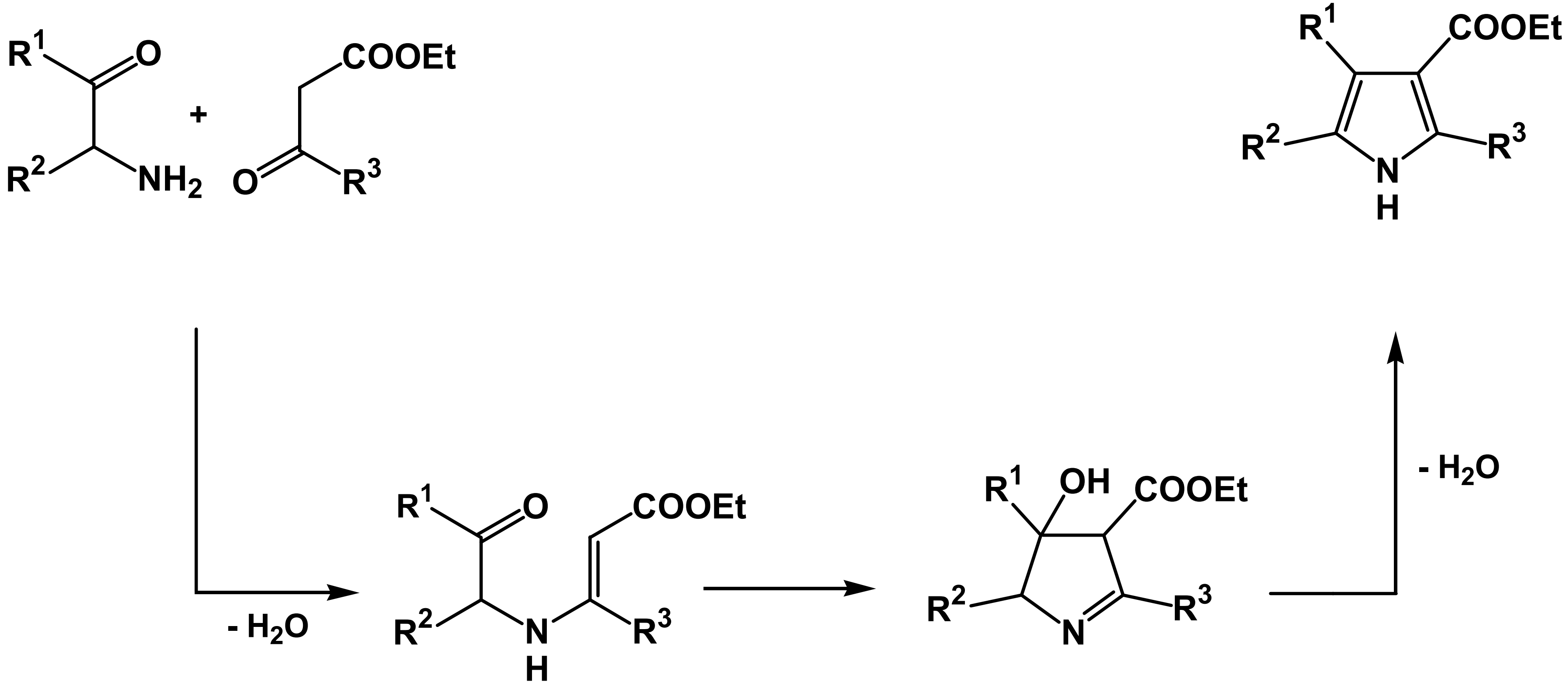


Arthur Rudolf Hantzsch

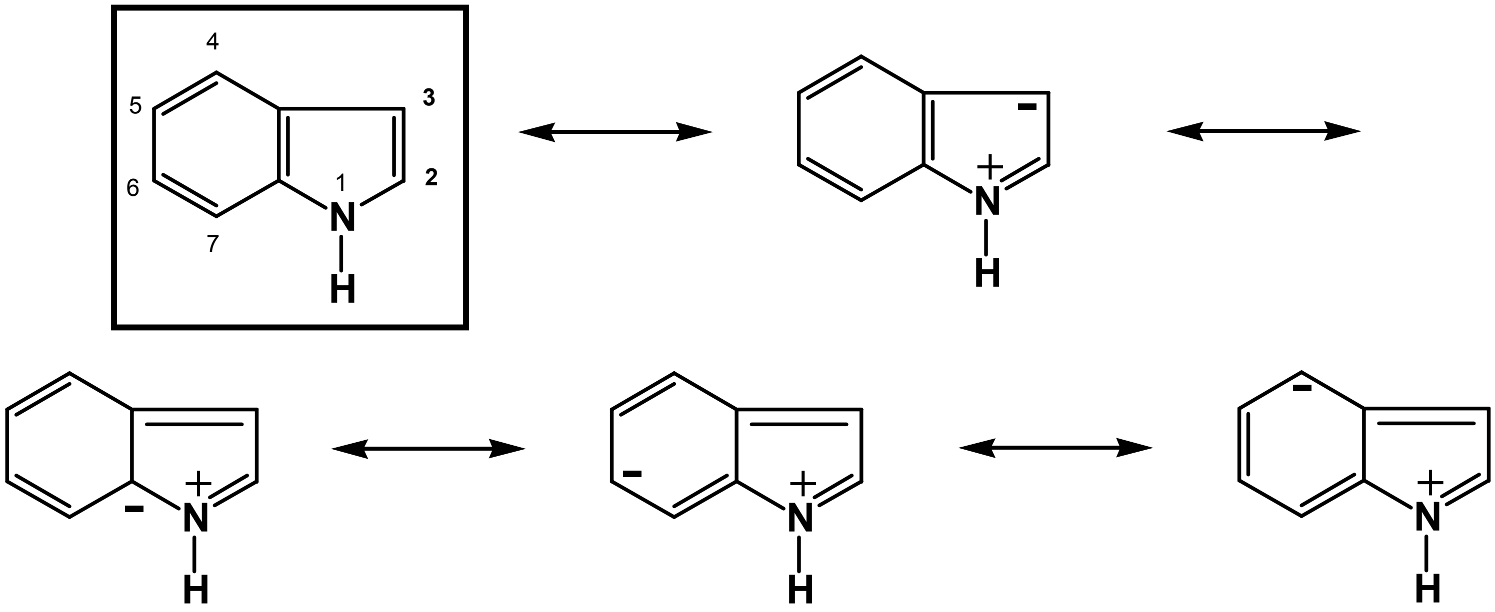
(Dresda, 1857 - Dresda 1935)

- Hantzsch studiò al Politecnico di Dresda e ottenne il dottorato a Würzburg. Fu professore di chimica organica al Politecnico di Zurigo, all'Università di Würzburg e all'Università di Lipsia. Notevoli gli studi di stereochimica e di chimica eterociclica (sintesi della piridina nel 1882, del cumarone nel 1886 e del tiazolo nel 1889). Si devono a lui le prime regole razionali di nomenclatura degli eterocicli.

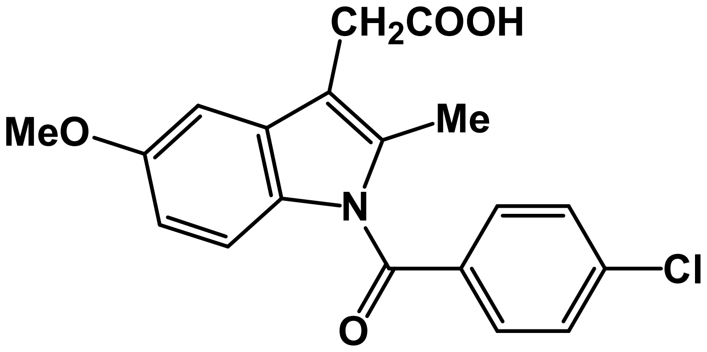
Pirrolo: sintesi di Knorr



Indolo

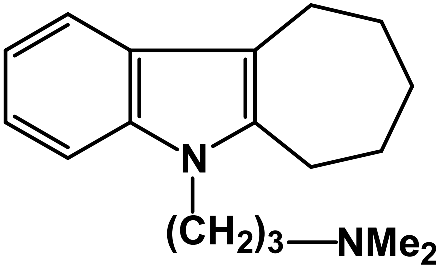


Alcuni derivati indolici importanti



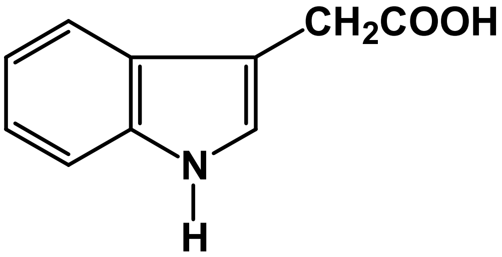
Indometacina

antinfiammatorio



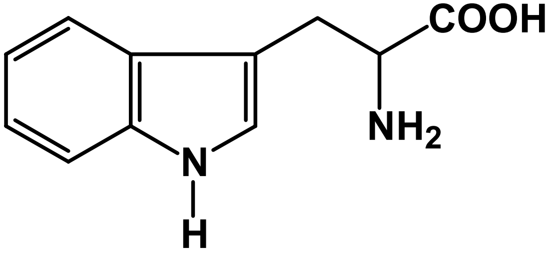
Iprindolo

antidepressivo



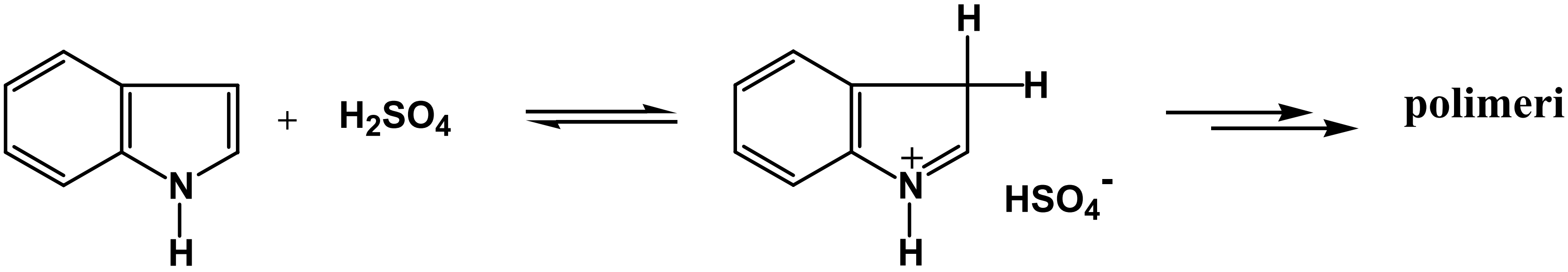
Acido indol-3-acetico

(eteroauxina) fitoormone



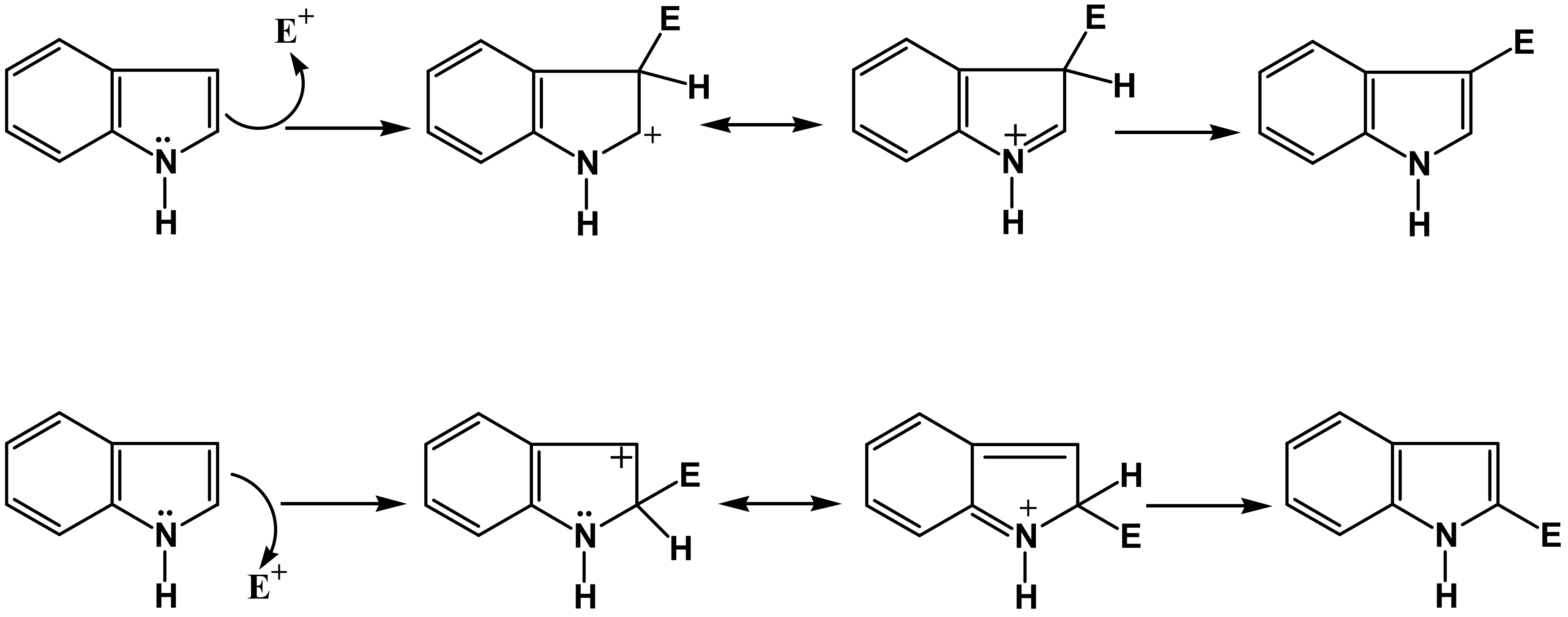
Triptofano

Indolo: protonazione



Le reazioni elettrofile dell’indolo

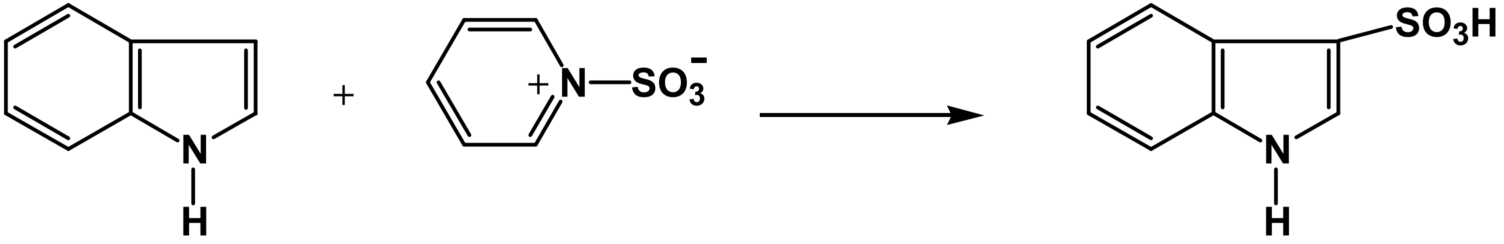
- **La posizione 3 è favorita!**



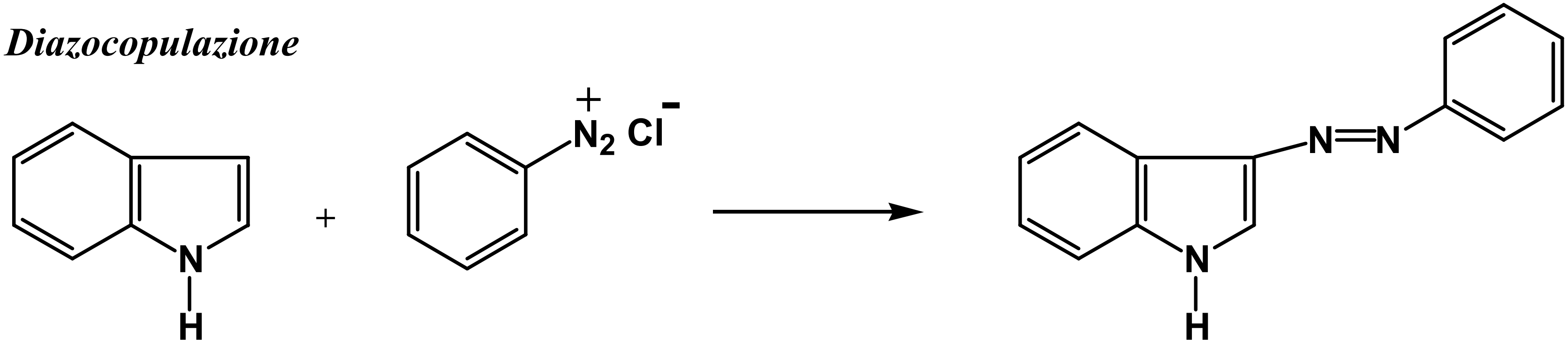
- **Se la posizione 3 è occupata, la reazione avviene in 2 e poi in 6**

Reazioni elettrofile

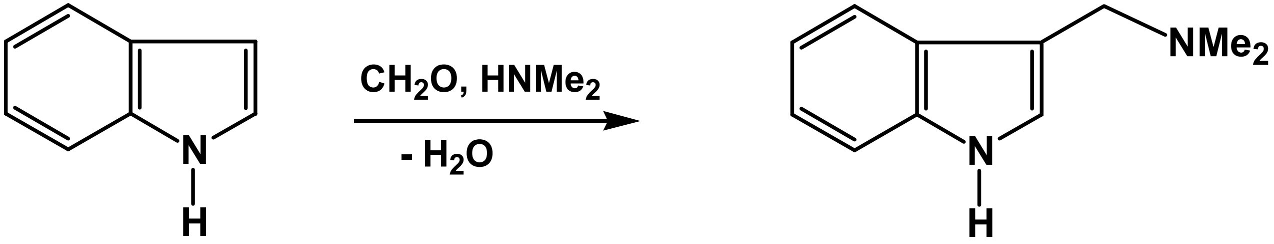
Solfonazione



Diazocopulazione



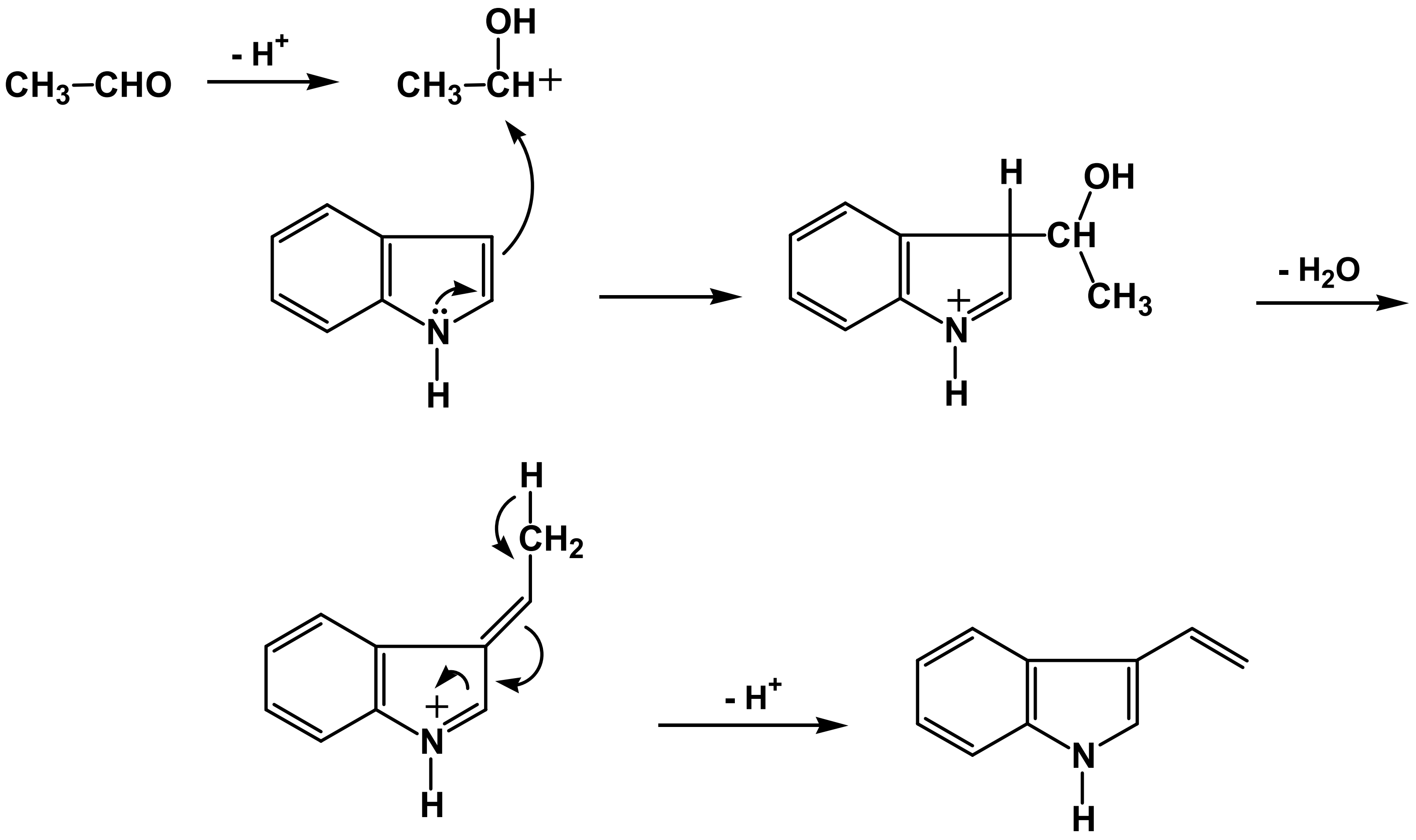
Reazione di Mannich



Gramina

(3-dimetilamminometilindolo)

Esercizio: L'indolo reagisce con l'acetaldeide in presenza di un catalizzatore acido. Cosa si ottiene?

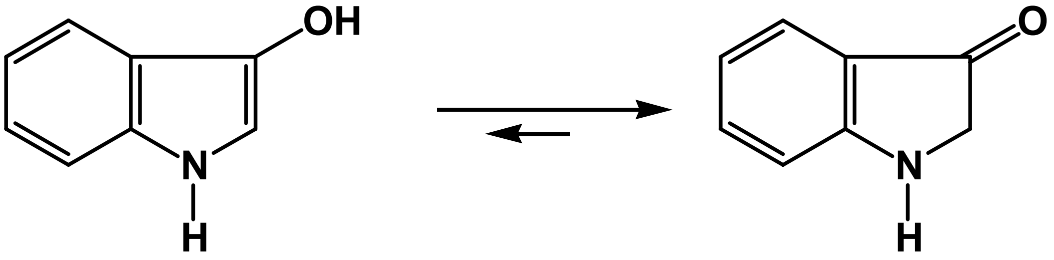


Derivati dell’indolo: indossile e ossindolo

Indossile

(3-Idrossindolo)

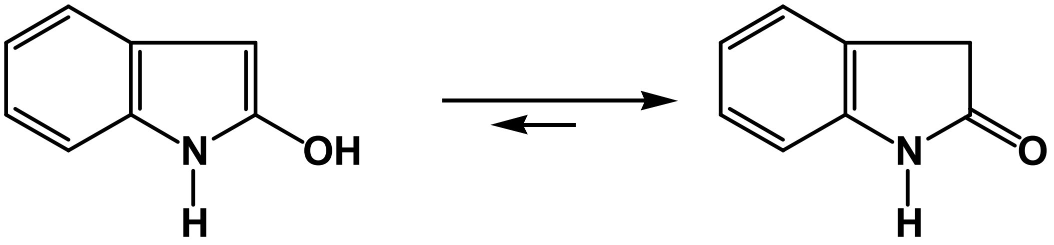
(Indolin-3-one)



Ossindolo

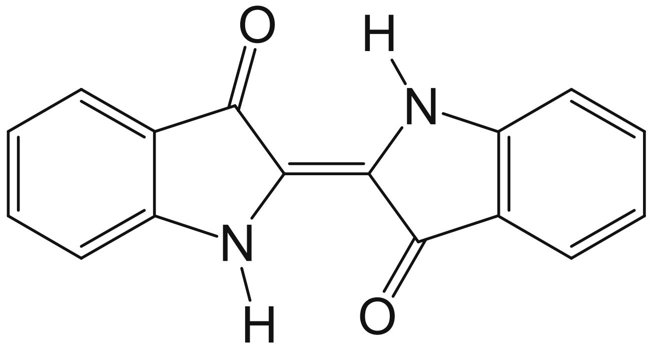
(2-Idrossindolo)

(Indolin-2-one)

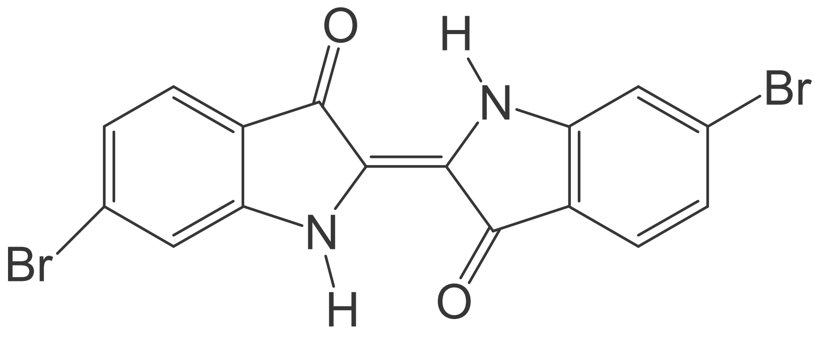


Indaco

Molecole relativamente piccole, ma con gruppi funzionali polari che consentono formule di risonanza con separazione di carica sono colorate. Un esempio è l'indaco, usato anche per tingere i blue jeans. (Prova a scrivere tutte le formule di risonanza dell'indaco!)



Porpora



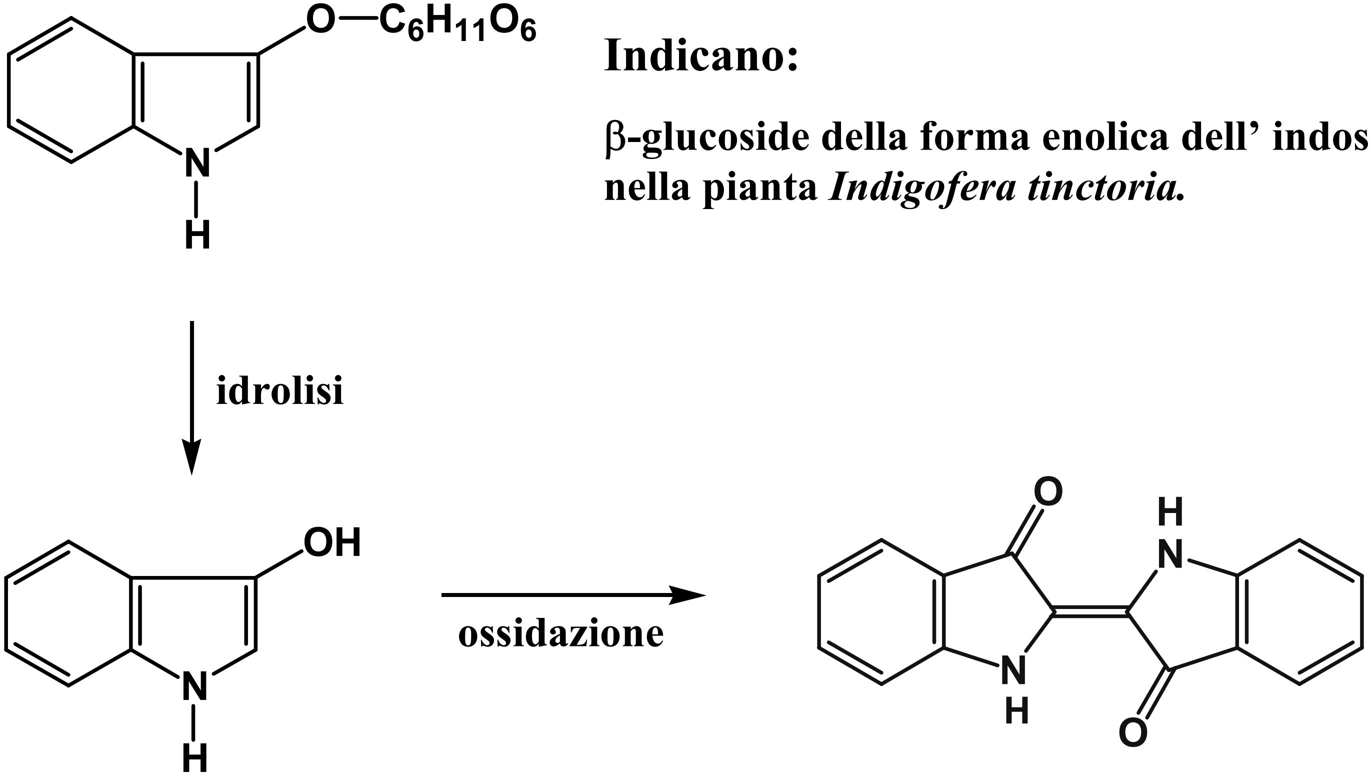
6,6’-Dibromoindaco

Un derivato dell‘indaco, *la Porpora di Tiro* degli antichi, è il 6,6'-dibromoindaco e si estrae da molluschi della specie *Murex brandaris*. Oggi l‘indaco non è un colorante costoso, ma la Porpora di Tiro era così cara che soltanto le classi sociali più ricche potevano permettersela.

L’indaco

Indicano:

β-glucoside della forma enolica dell’ indossile contenuto nella pianta *Indigofera tinctoria.*

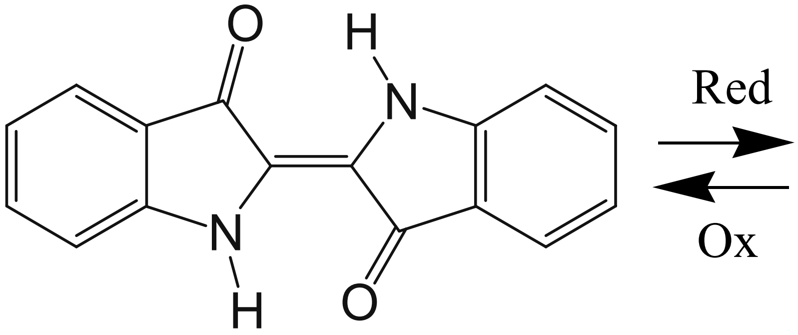


Indaco

Indigofera tinctoria

Arbusto alto fino a 120 cm, originario dell'Asia e importato negli altri continenti per la produzione dell'Indaco. La pianta, tagliata e legata in mazzi, è messa in una vasca e lasciata fermentare: dopo 18 ore si separa il liquido dai rami e dalle foglie. Il liquido, agitato, deposita una melma blu che viene separata e asciugata. La polvere così ottenuta è il colorante.

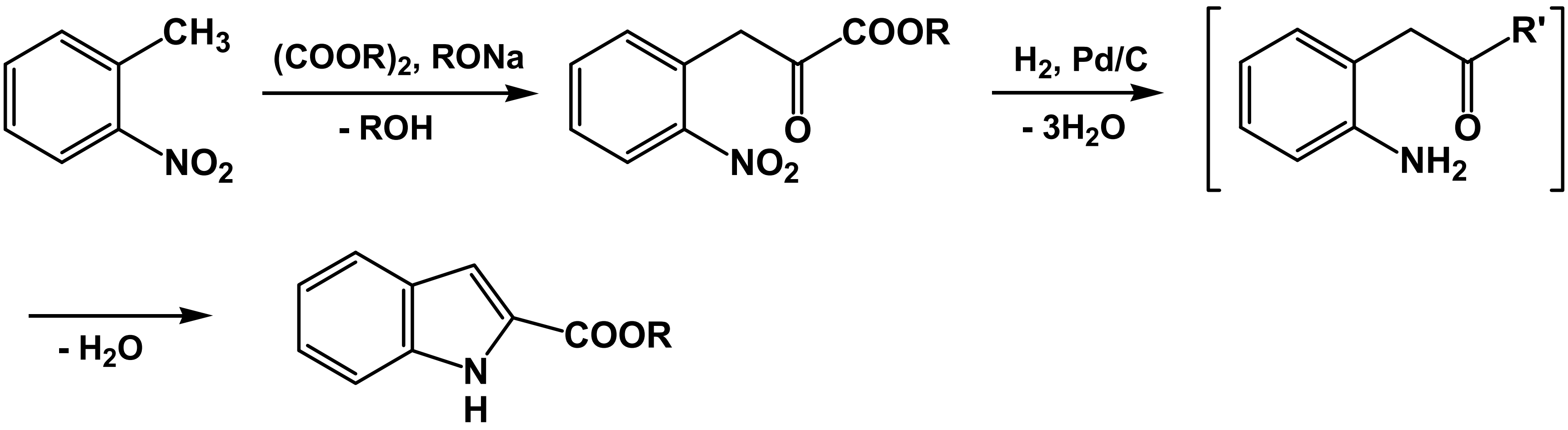
Coloranti al tino: sono insolubili, ma possono essere ridotti a una forma solubile spesso incolore. Si impregna la fibra e si ossida: il colore ricompare e il colorante resta incorporato nella fibra. L'indaco è un esempio classico.



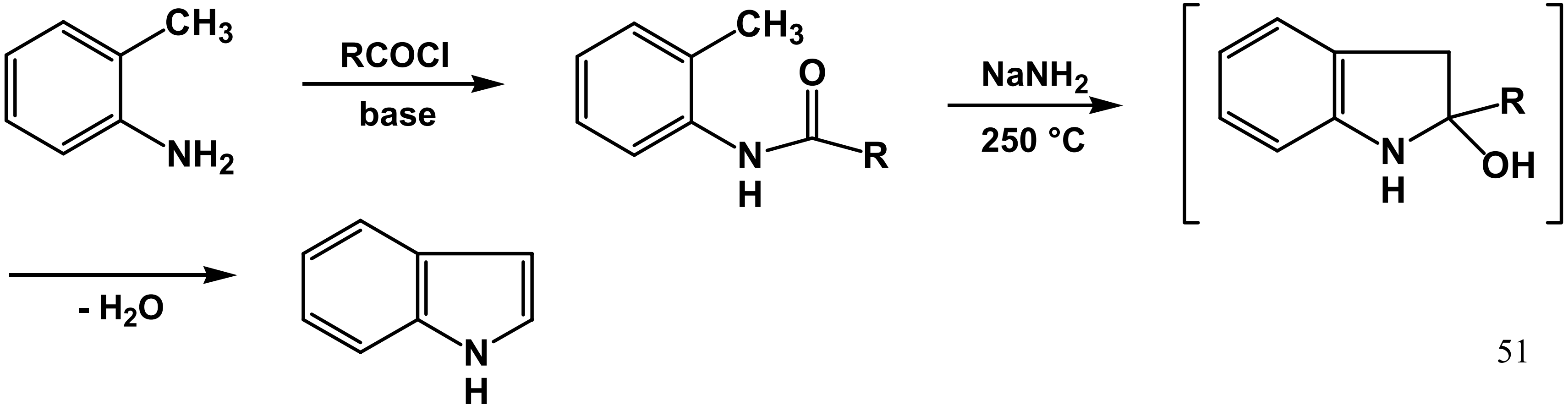
indaco
(insolubile)

Indolo: sintesi di Reissert e di Madelung

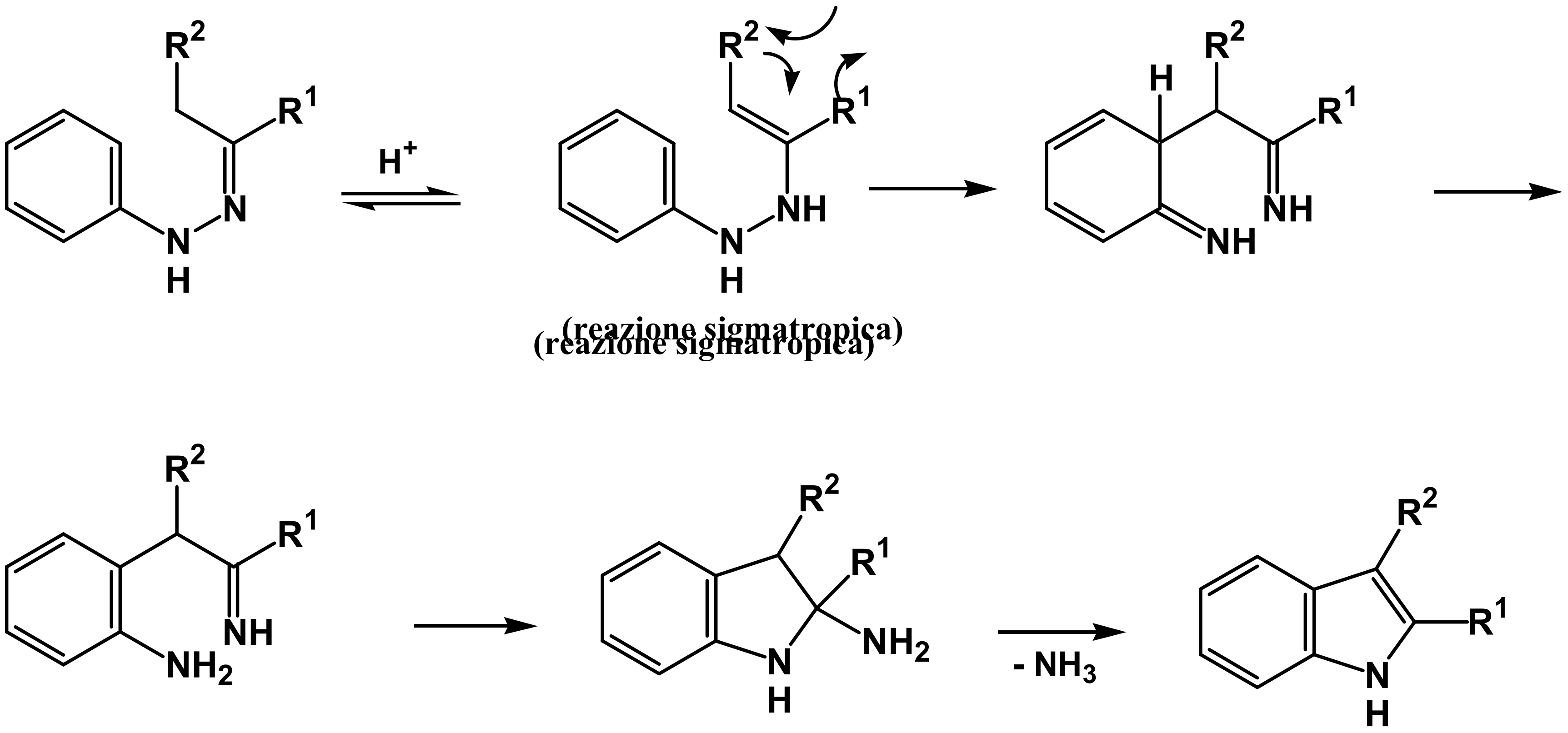
- *sintesi di* Reissert



- *sintesi di* Madelung



Indolo: sintesi di Fischer (1883)

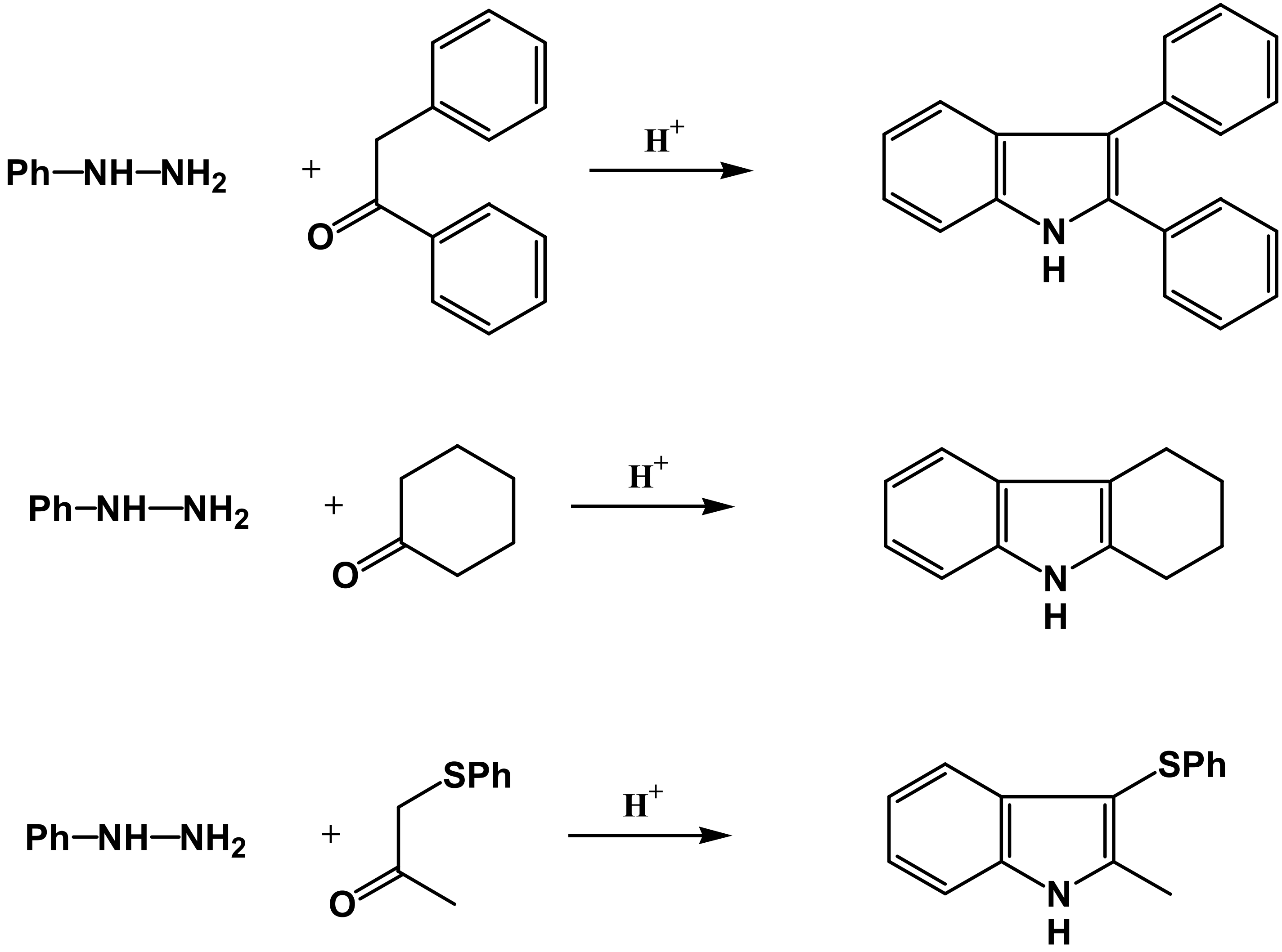


(reazione sigmatropica)

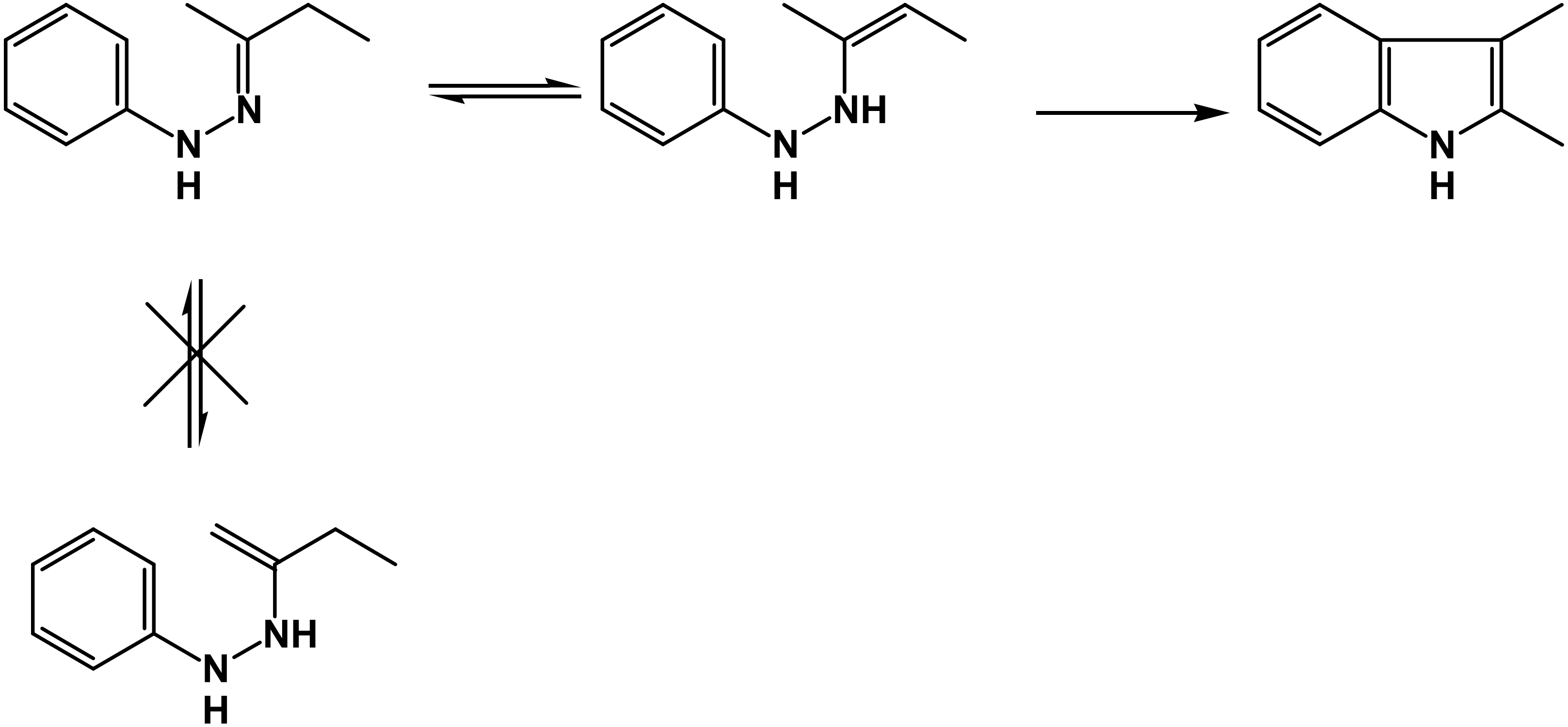
(reazione sigmatropica)

H$^+$: H_2SO_4, ac. polifosforico, CH_3COOH, HCl in EtOH, $ZnCl_2$, BF_3, ecc.

Alcuni esempi di sintesi di Fischer



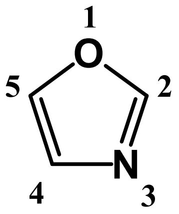
La sintesi di Fischer su chetoni *non* simmetrici



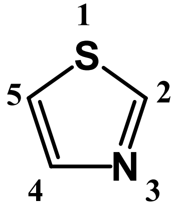
Emil Fischer (1852 - 1919)

- Laureato a Strasburgo, allievo e collaboratore di von Baeyer, scoprì nel 1874 la fenilidrazina e ne descrisse le caratteristiche. Fu docente a Monaco, a Erlangen, a Würzburg e infine a Berlino. Vinse il premio Nobel per la chimica nel 1902. Affrontò molti problemi chimici con successo, ma la sua fama è dovuta soprattutto ai lavori sulle purine e sugli zuccheri. Tra il 1882 e il 1906 dimostrò che varie sostanze, allora poco note come l'adenina, la xantina, la caffeina, l'acido urico e la guanina sono tutte correlate e hanno una struttura comune, la purina, non nota allora, che egli sintetizzò nel 1898. Nel 1984 iniziò il monumentale lavoro sugli zuccheri. Sfruttando la formazione degli osazoni dimostrò la relazione tra glucosio, fruttosio e mannosio, stabilì la stereochimica e l'isomeria di tutti gli zuccheri allora noti e predisse l'esistenza degli altri, applicando la teoria del carbonio asimmetrico. Mise a punto processi di isomerizzazione, di degradazione e di sintesi e il suo più grande successo fu la sintesi di glucosio, fruttosio e mannosio partendo dal glicerolo.

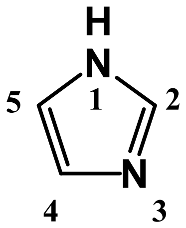
1,3-Azoli: Ossazolo - Tiazolo - Imidazolo



Ossazolo (1,3-ossazolo)

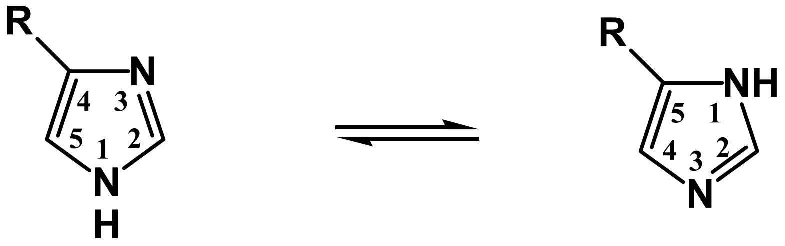


Tiazolo (1,3-tiazolo)



Imidazolo

Tautomeria **nell'imidazolo**

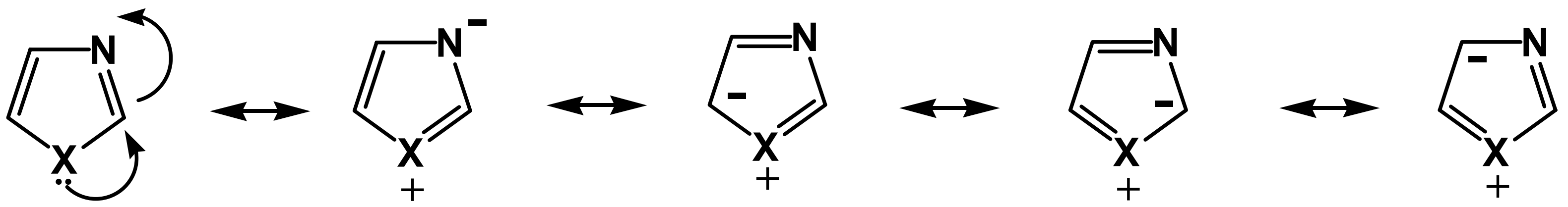


4-alchilimidazolo

5-alchilimidazolo

Ossazolo - Tiazolo - Imidazolo

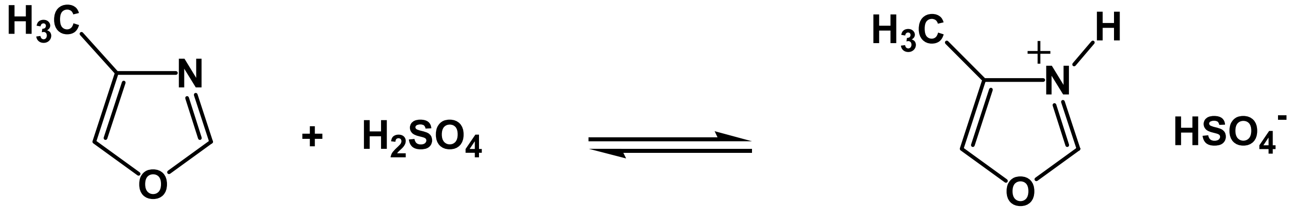
Mesomeria



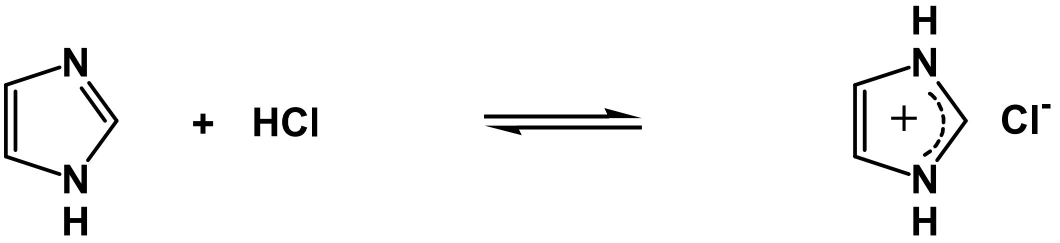
X = O, NH, S

Ossazolo - Tiazolo - Imidazolo

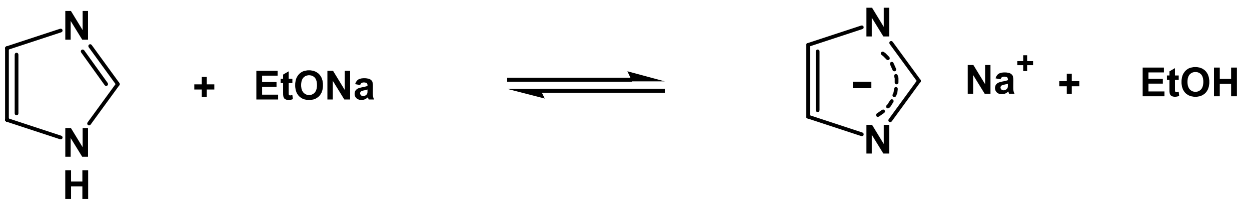
Reazioni con acidi e basi



$pK_a = 0.8$



$pK_a = 0.7$

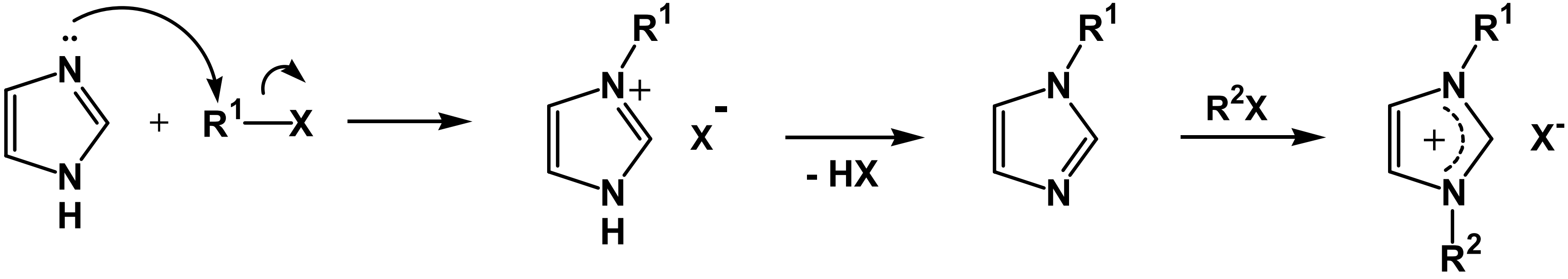


$pK_a = 14.5$

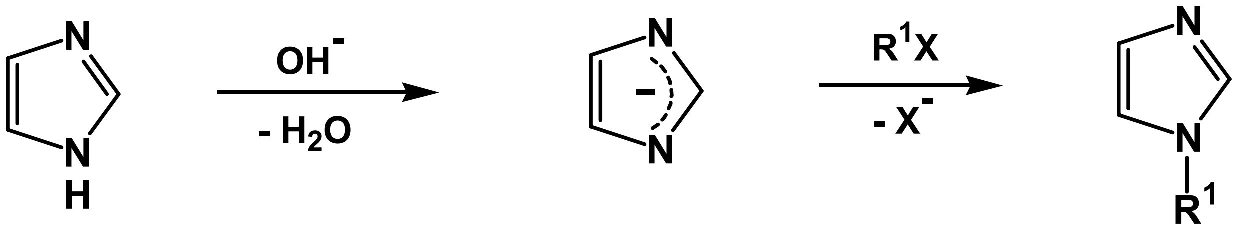
Imidazolo

Reazioni di alchilazione

- *in assenza di basi*

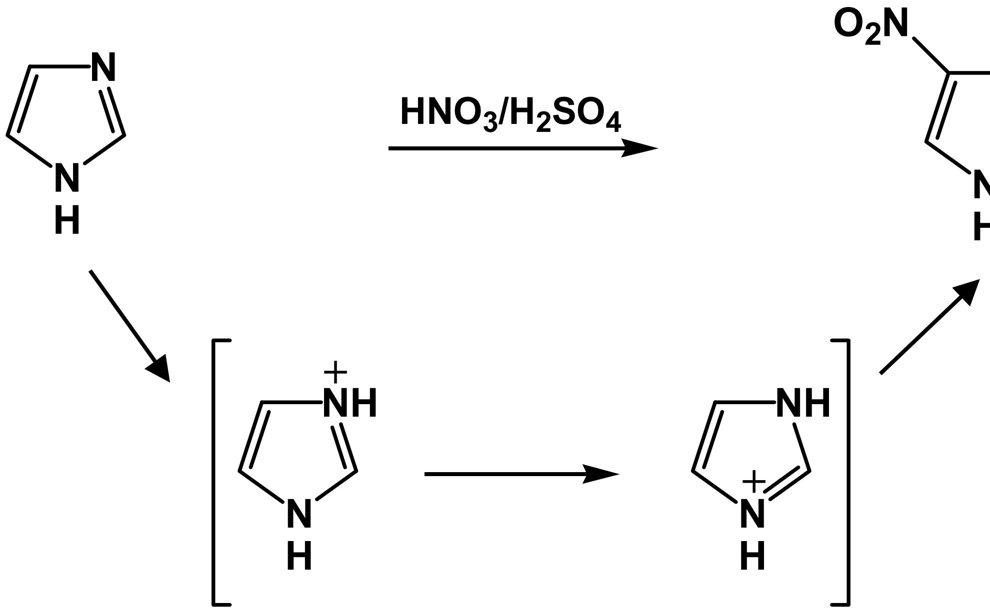


- *in presenza di basi*



Ossazolo - Tiazolo - Imidazolo

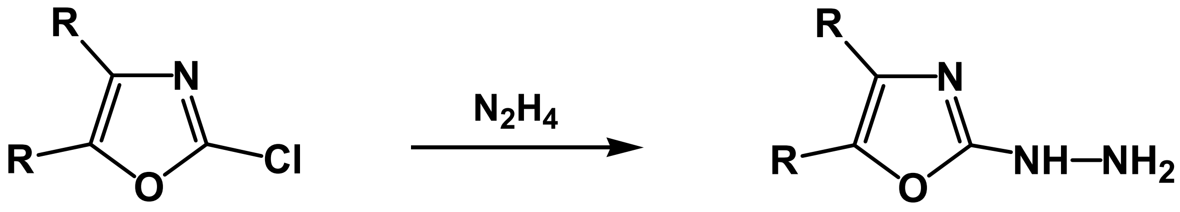
- **reazioni di sostituzione elettrofila:** **reazione *relativamente difficile***

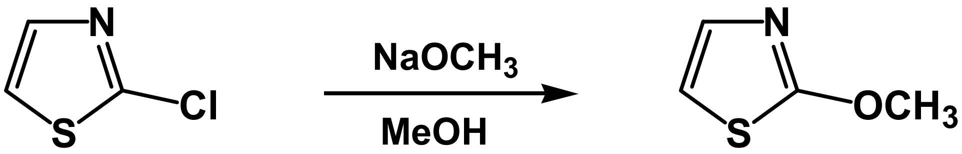


Specie che reagisce

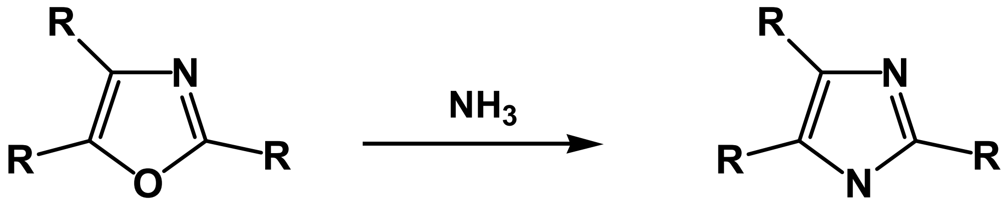
Ossazolo - Tiazolo - Imidazolo

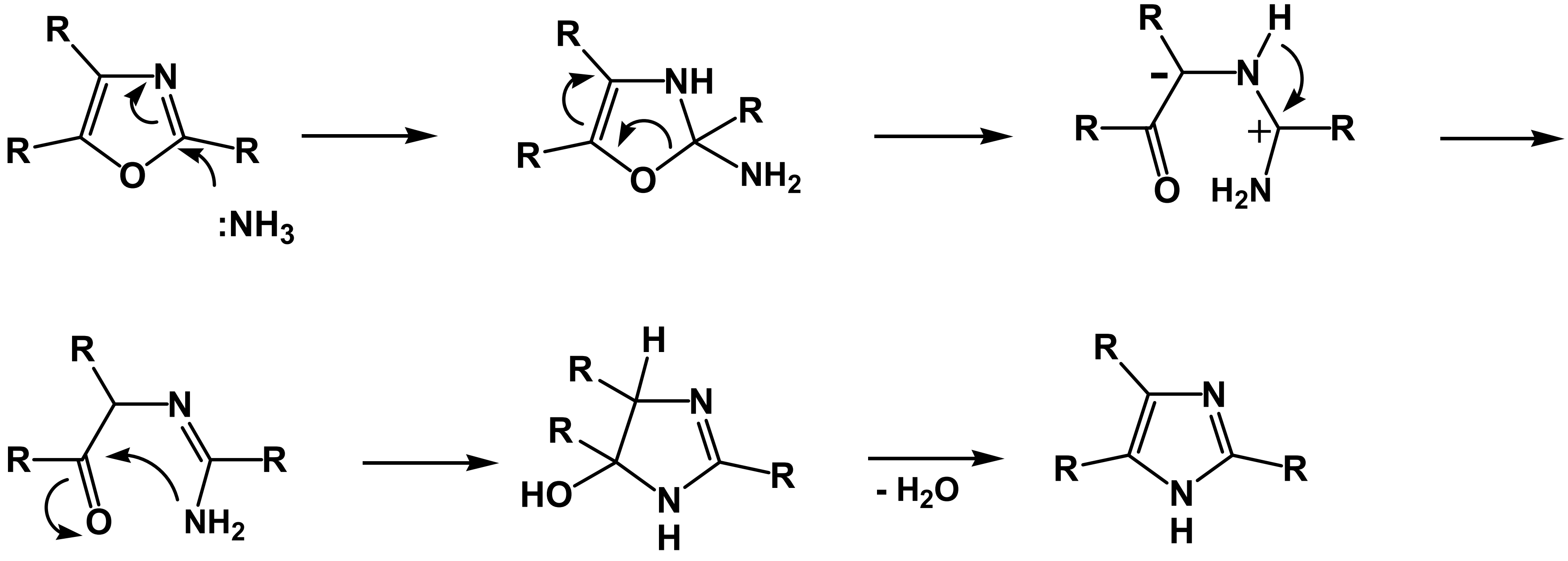
- **Reazioni di sostituzione nucleofila**



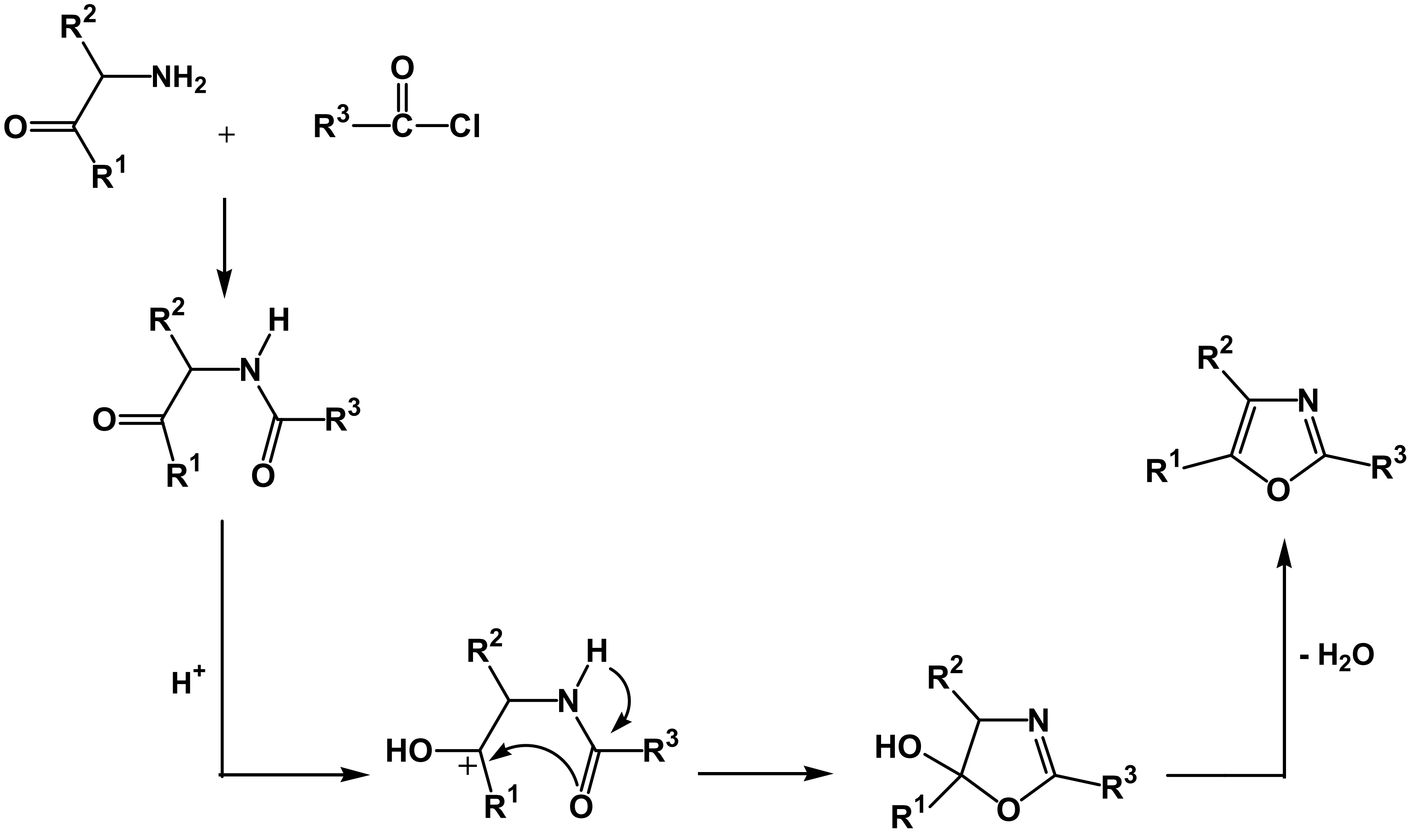


Esercizio. Suggerire un meccanismo per la seguente reazione:

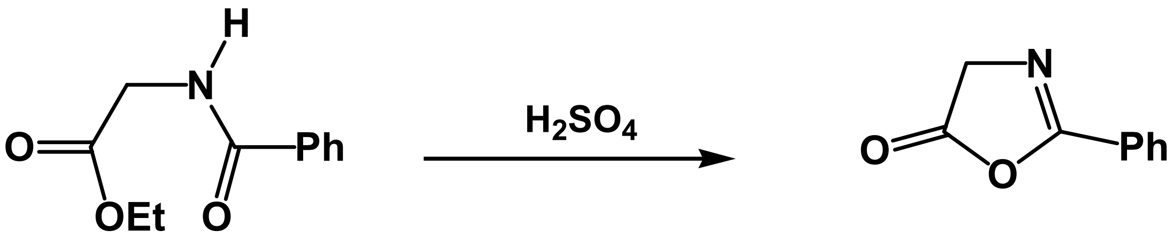




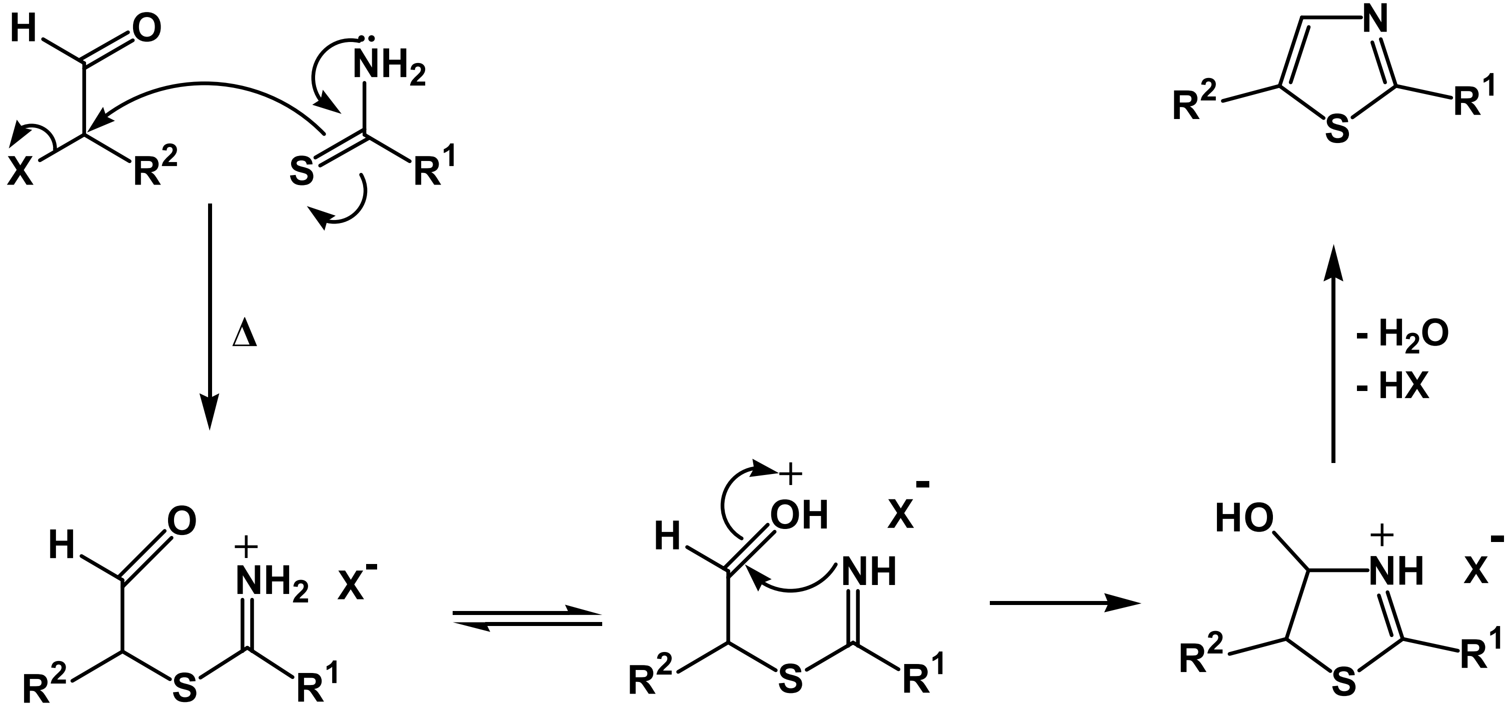
Ossazolo: sintesi di Robinson-Gabriel



Esercizio: quale prodotto si ottiene dalla sintesi di Robinson-Gabriel se la si applica al *N*-benzoilglicinato d'etile?

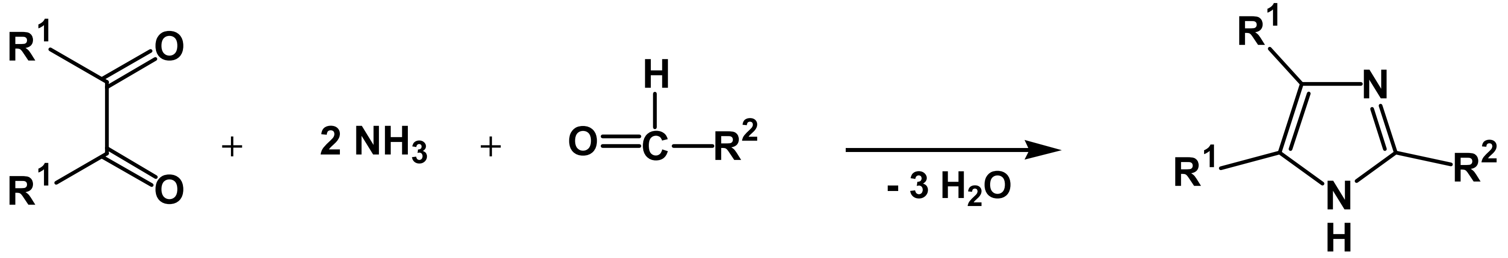


Tiazolo: sintesi di Hantzsch

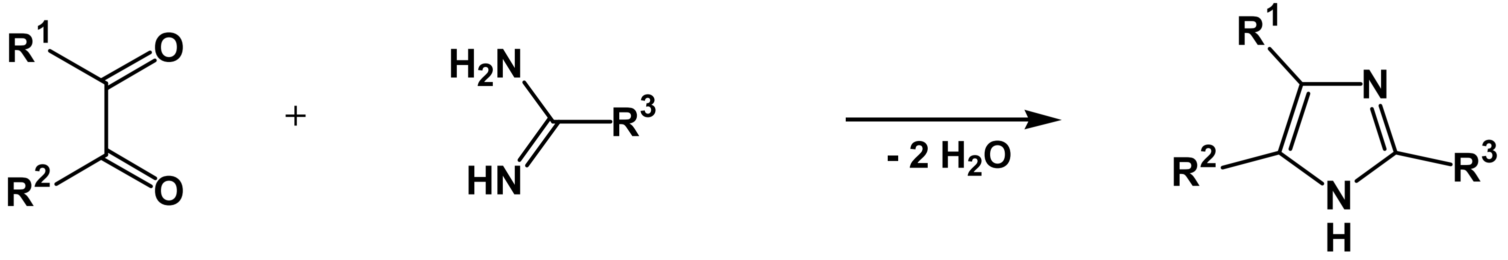


Sintesi dell’imidazolo

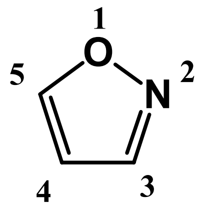
A)



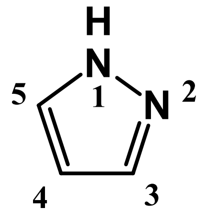
B)



Isossazolo e Pirazolo

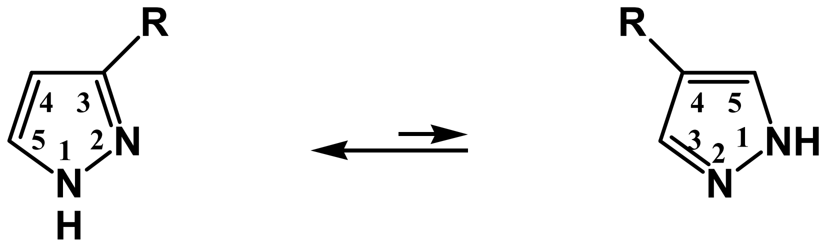


Isossazolo (1,2-ossazolo)

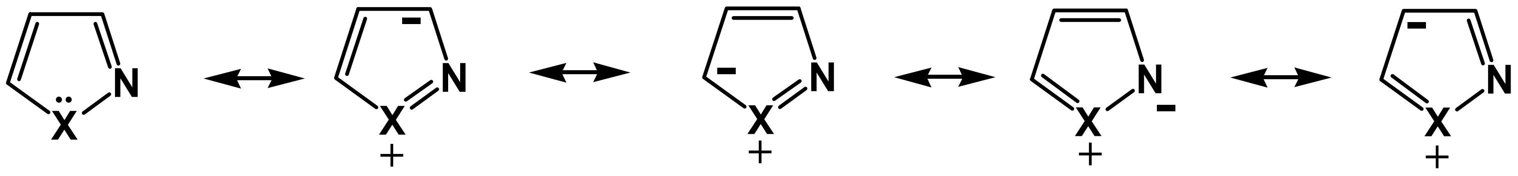


Pirazolo

***Tautomeria* nel pirazolo**



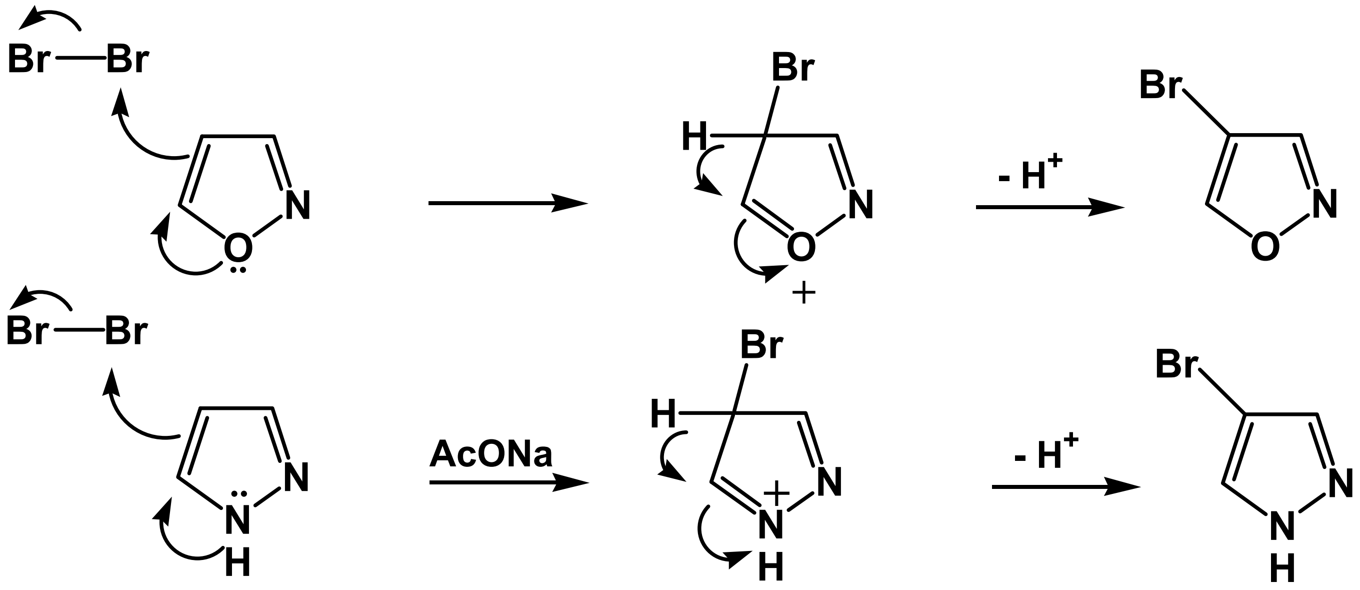
Isossazolo e Pirazolo



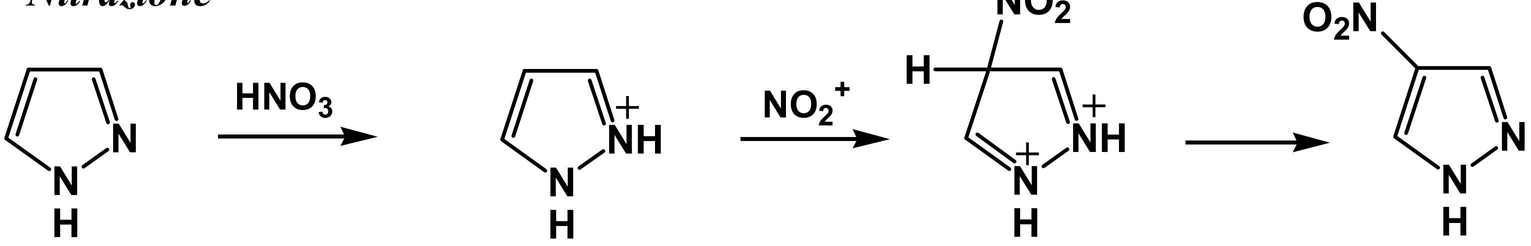
Isossazolo e Pirazolo

Reazioni di *sostituzione elettrofila*

- *Alogenazione*



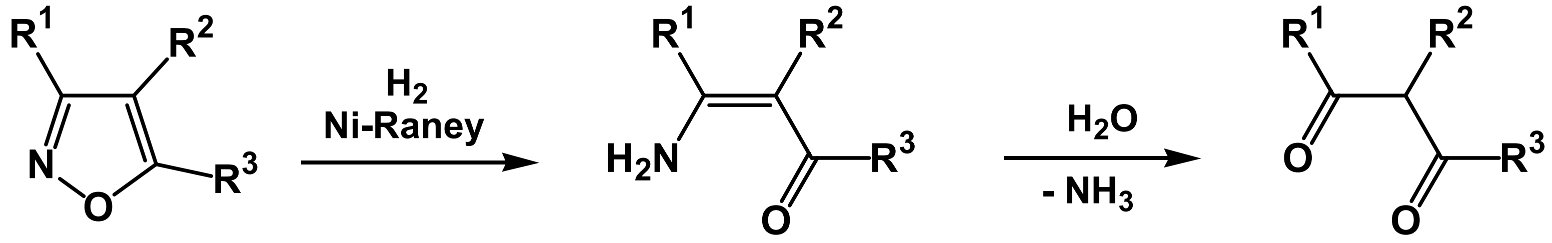
- *Nitrazione*



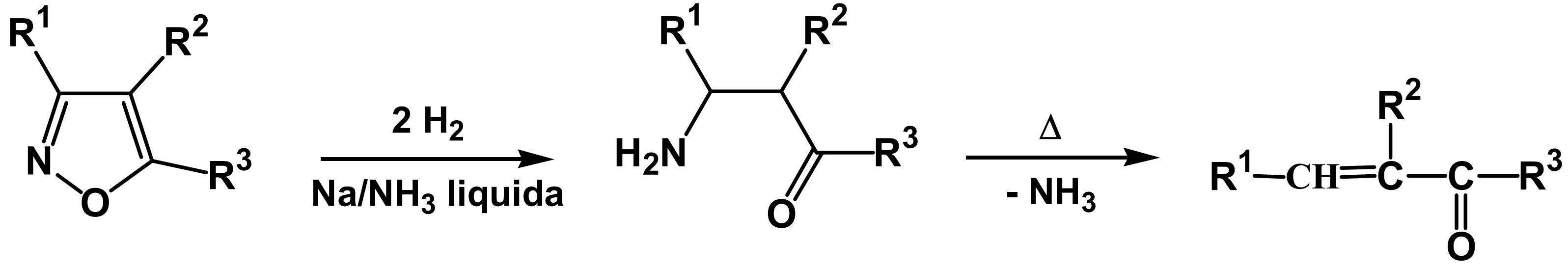
Isossazolo

Reazioni di apertura all'anello per via riducente

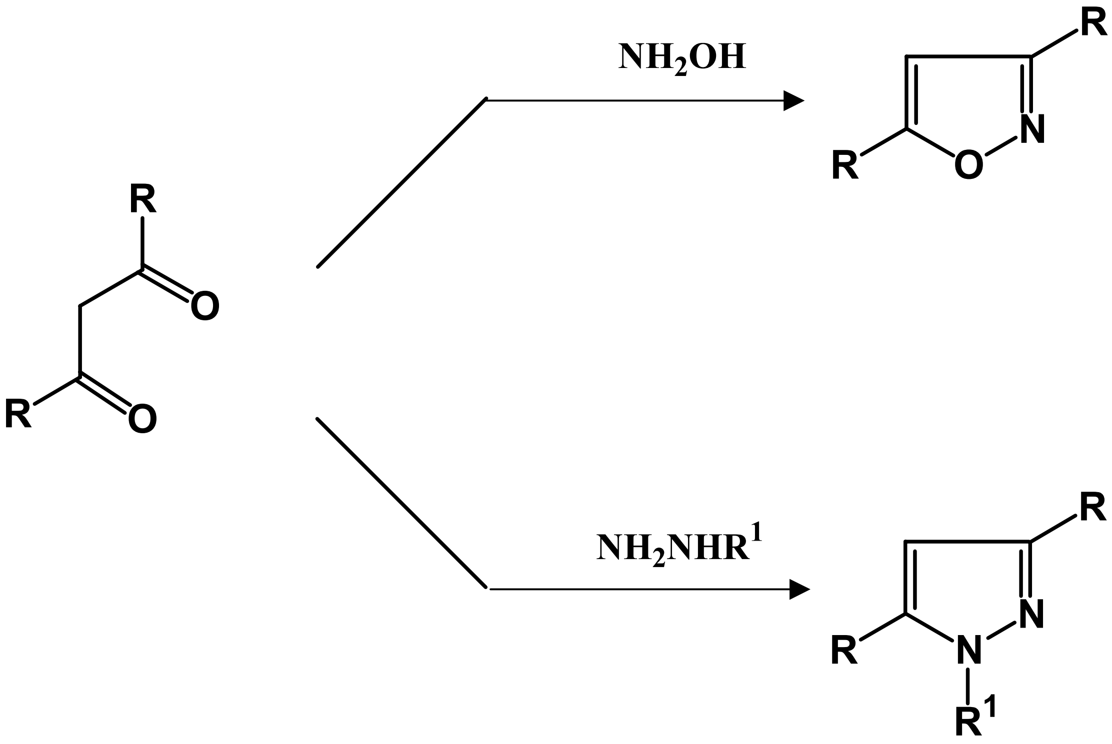
- **sintesi di β-dichetoni**



- **sintesi di chetoni α,β-insaturi**

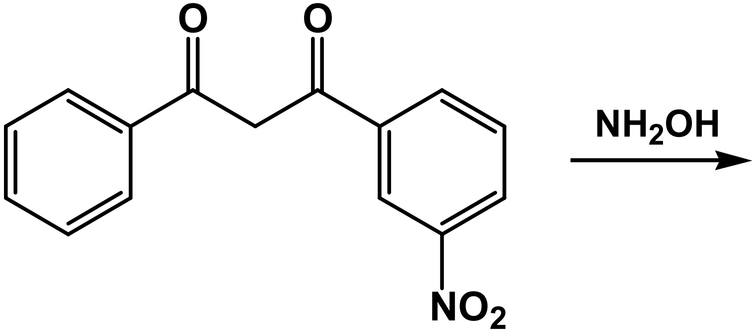


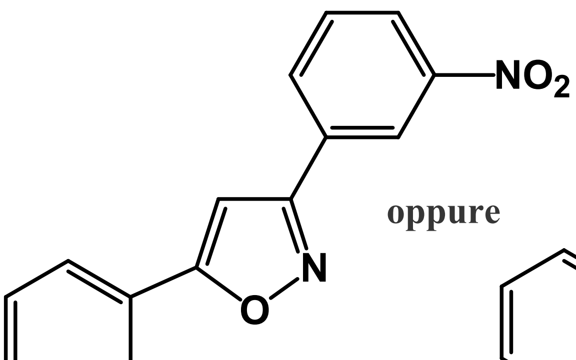
Isossazolo - Pirazolo: *sintesi*



Esercizio: scegliere il prodotto più probabile delle seguenti reazioni scrivendo il meccanismo

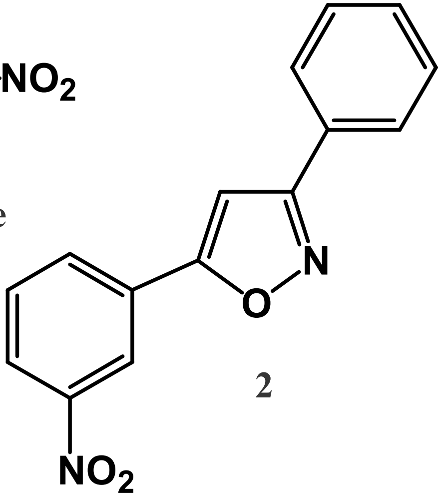
A)





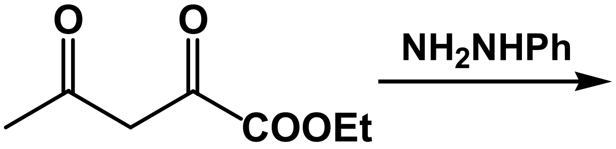
1

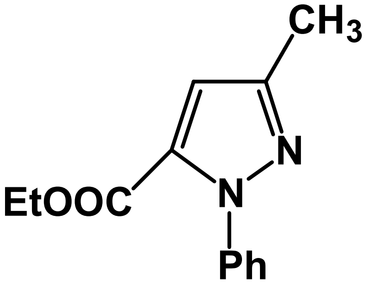
oppure



2

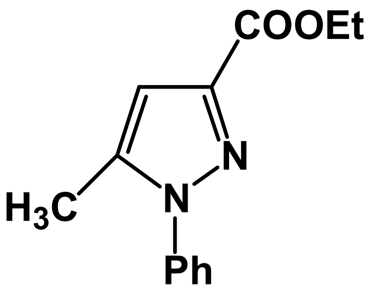
B)





3

oppure

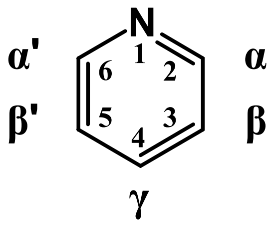


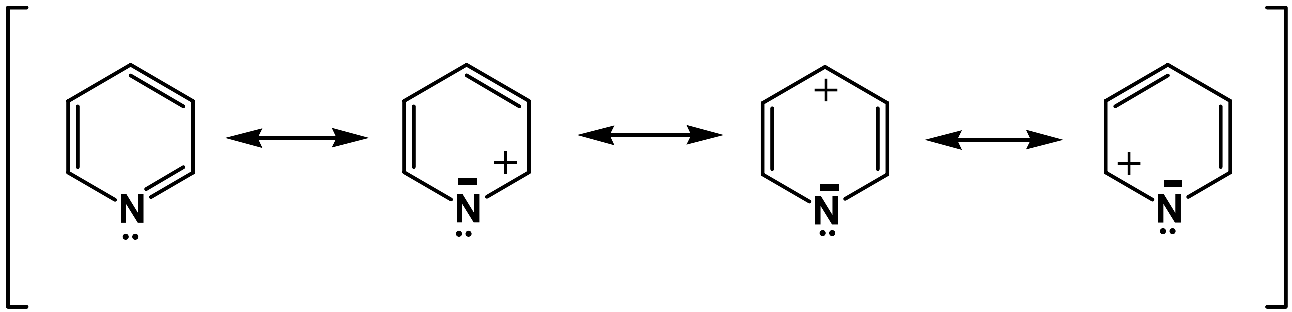
4

La condensazione del gruppo NH_2 è preferita sul CO più reattivo

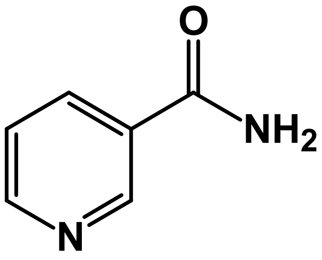
Risposta: A = 1; B = 4

Piridina

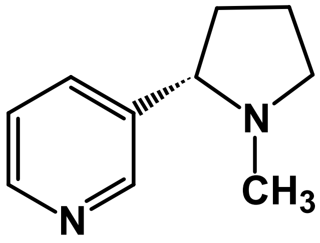




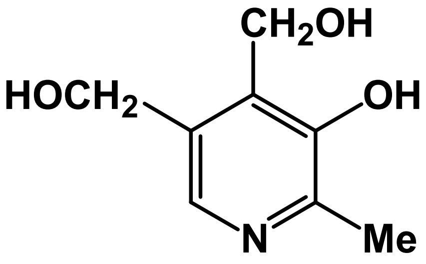
Alcuni derivati della piridina importanti



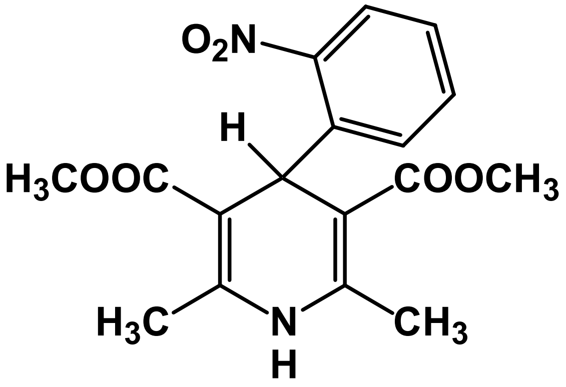
Nicotinammide



Nicotina

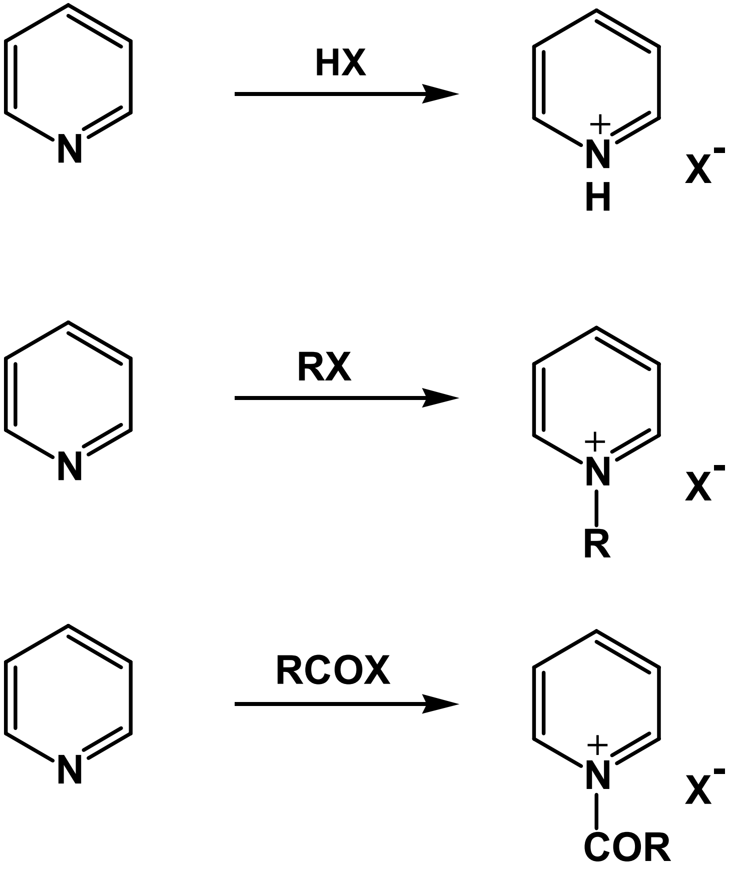


Piridossina
Vitamina B_6



Nifedipina

La piridina è una base e un nucleofilo!



Alogenuro di piridinio

$pK_a = 5.2$

Sale di alchilpiridinio

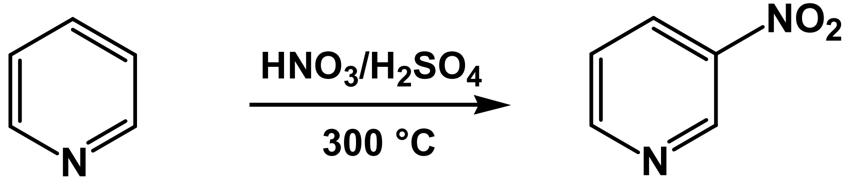
Sale di acilpiridinio

(agente acilante)

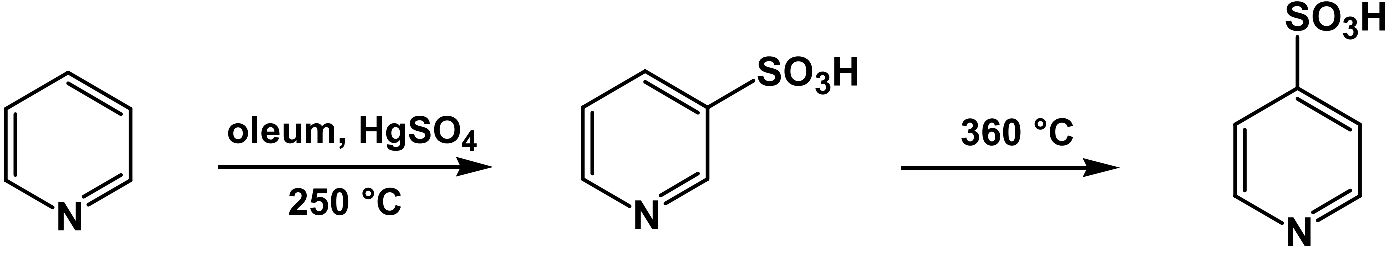
Reazioni di *sostituzione elettrofila*

- ***nitrazione***

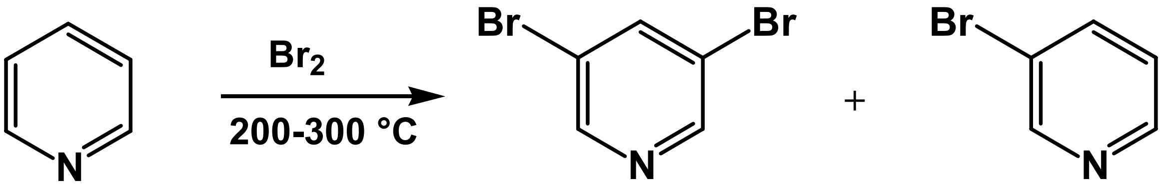
	Reattività
Benzene	**1**
Piridina	**10^{-10}**



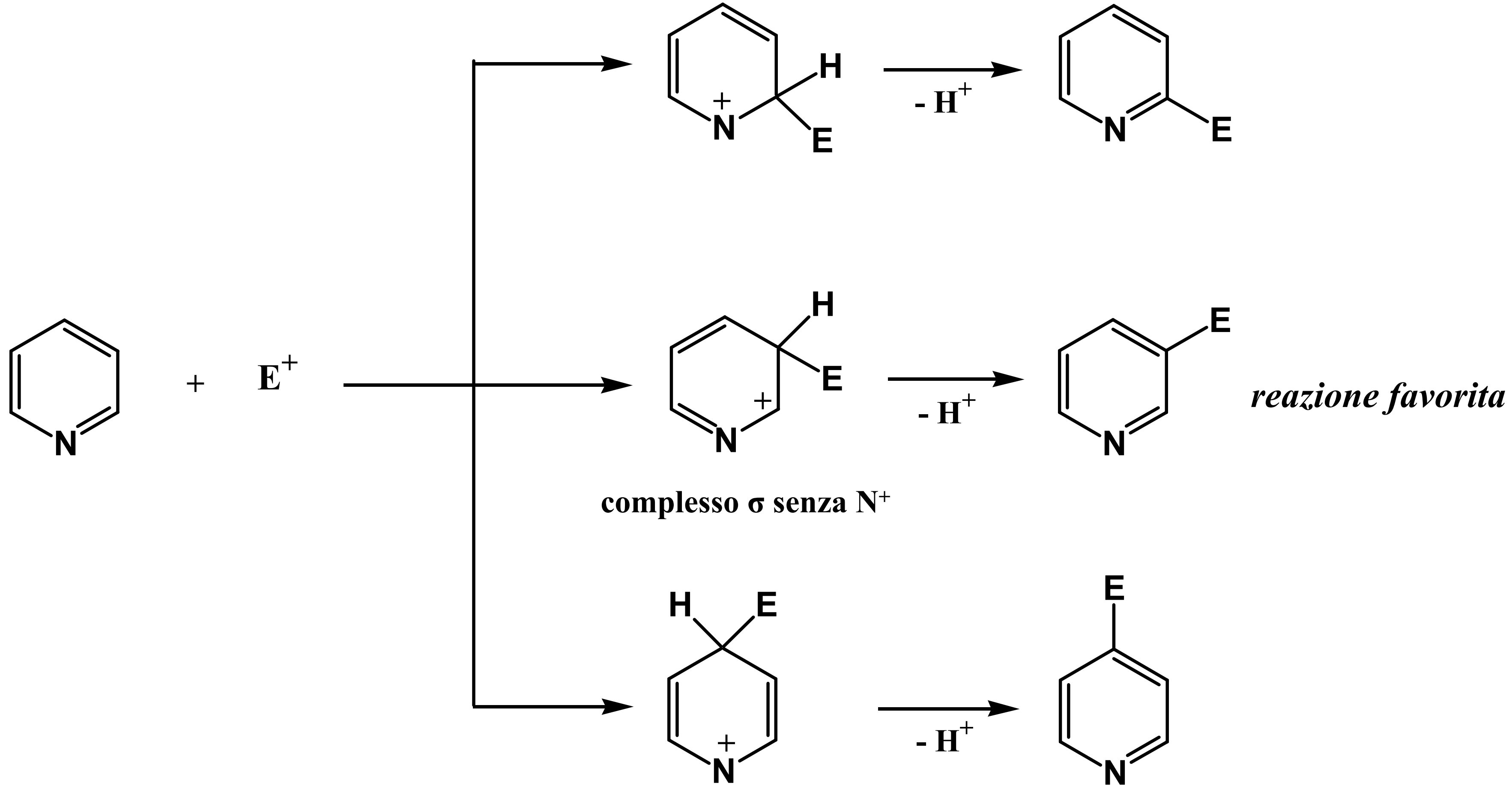
- ***solfonazione***



- ***bromurazione***



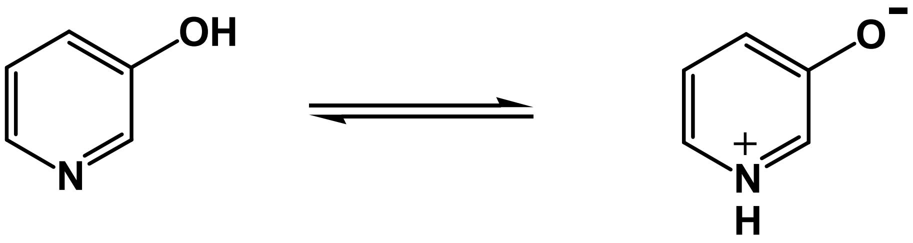
Reazioni di sostituzione elettrofila: *orientamento*

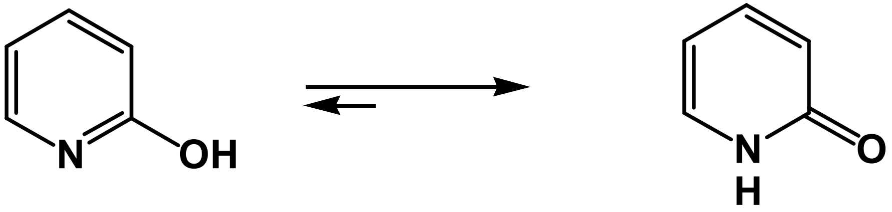


reazione favorita

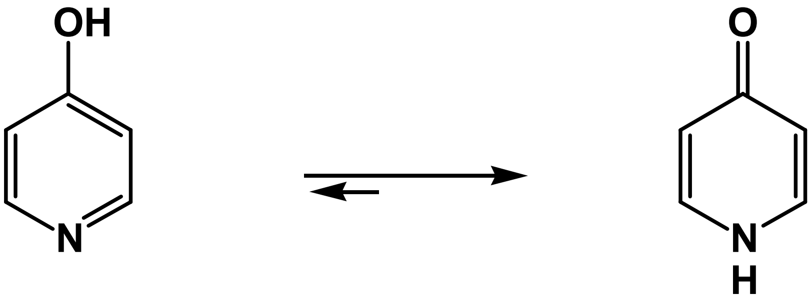
complesso σ senza N$^+$

Idrossipiridine



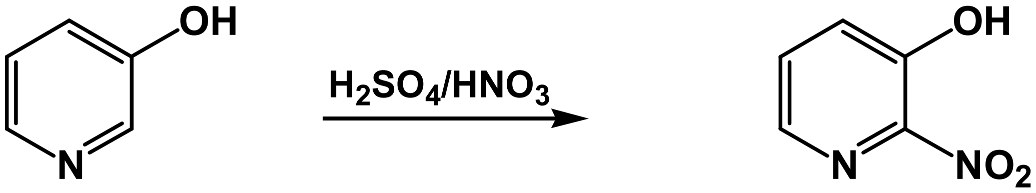


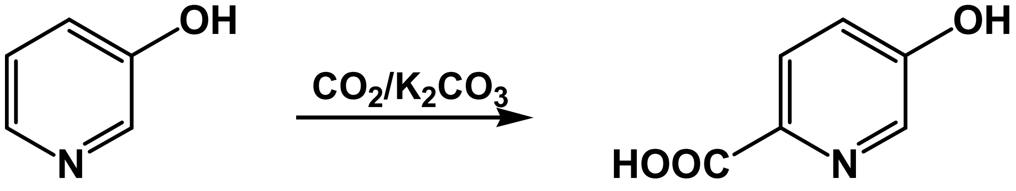
2-piridinone



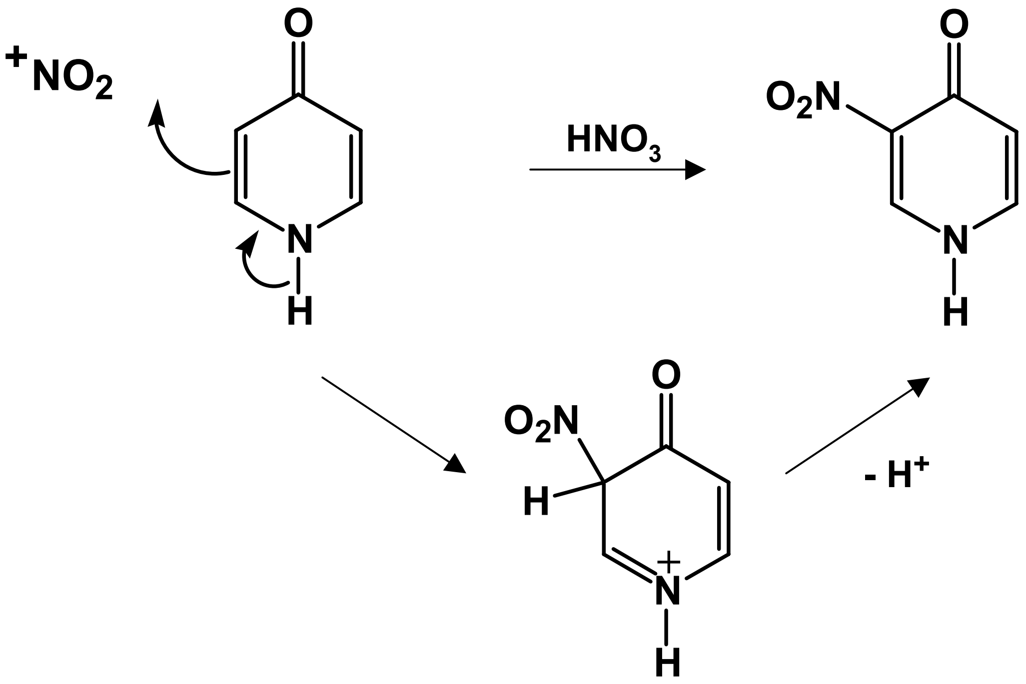
4-piridinone

Alcune reazioni di sostituzione elettrofila della 3-idrossipiridina

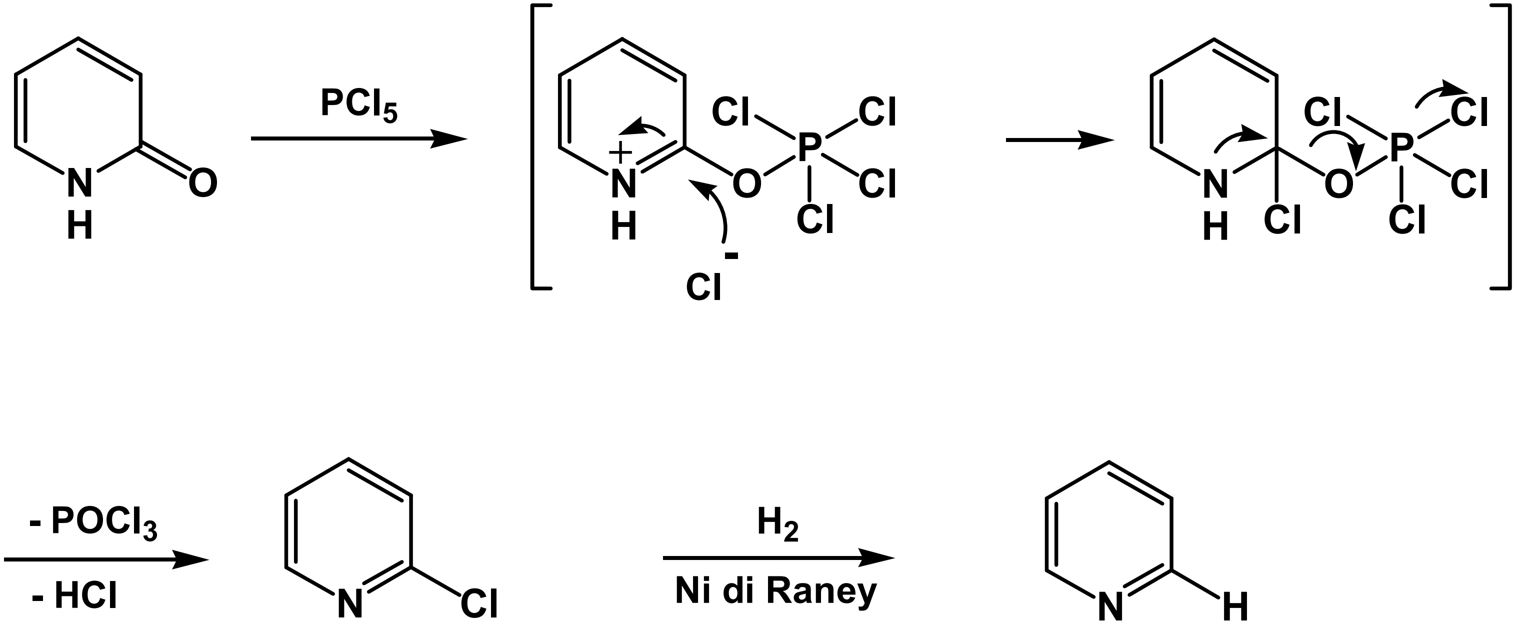




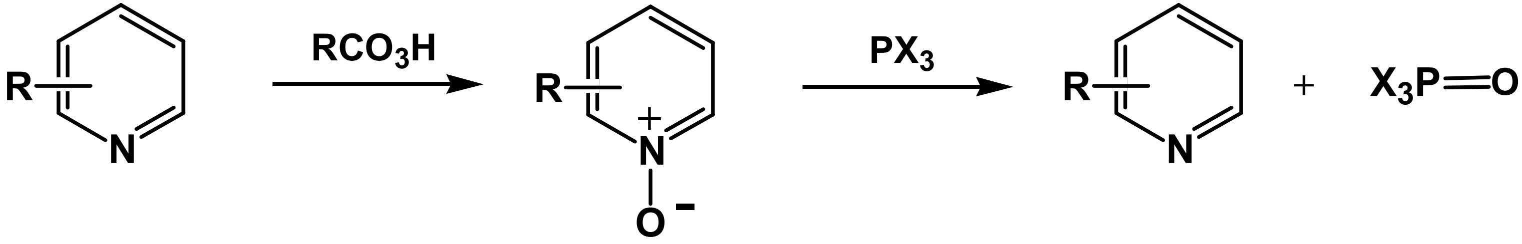
Sostituzioni elettrofile dei piridoni

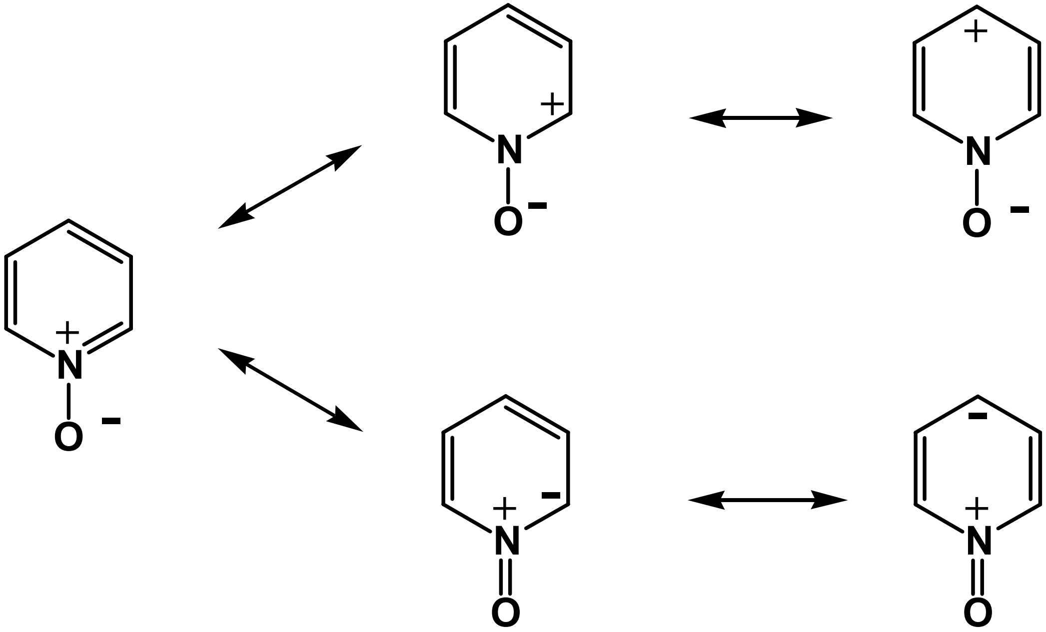


Dai piridoni alle alogenopiridine e alle piridine

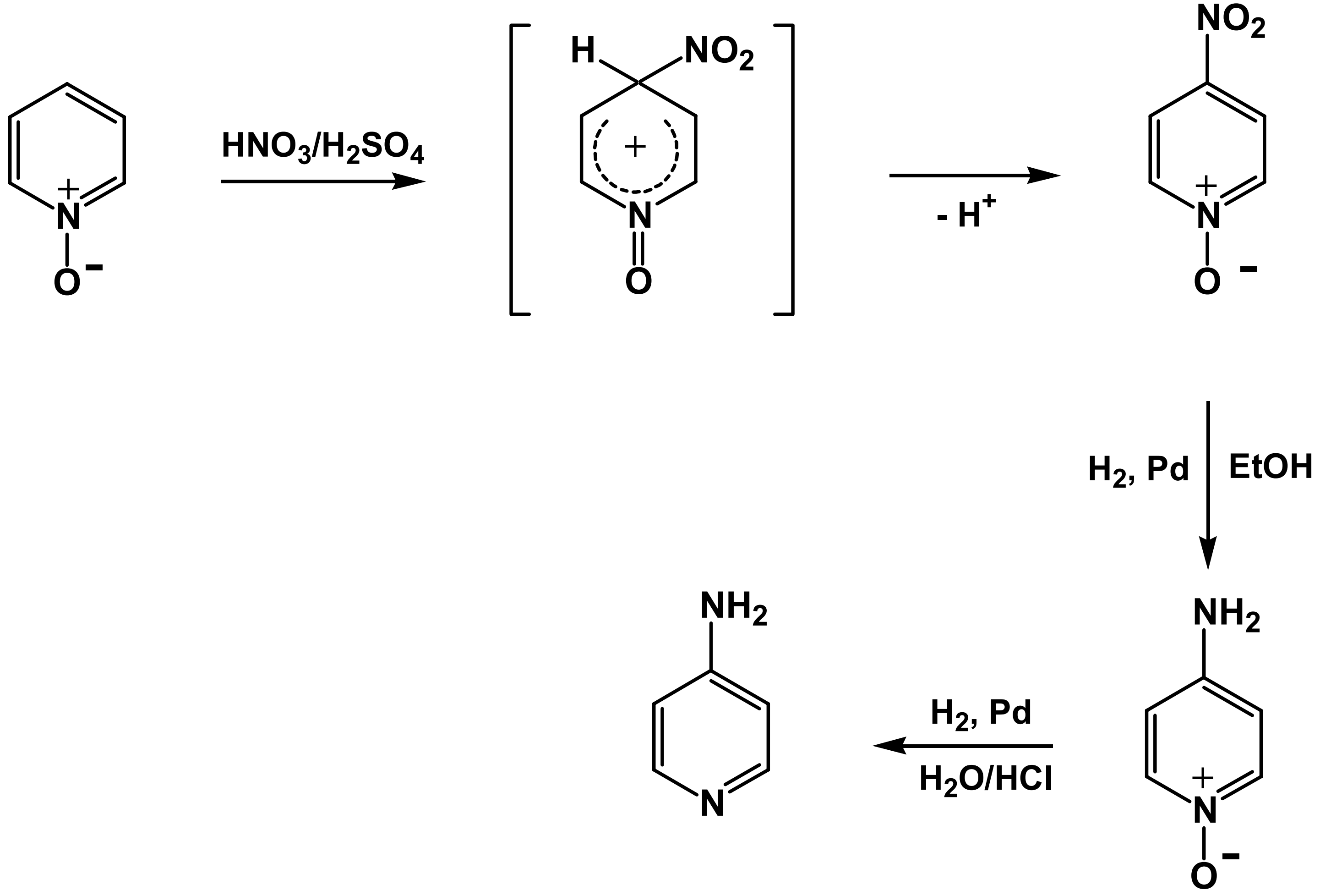


N-ossidi di piridina

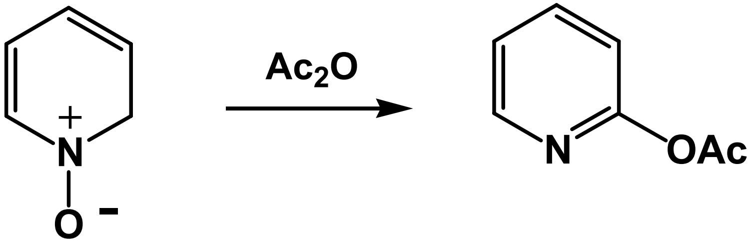


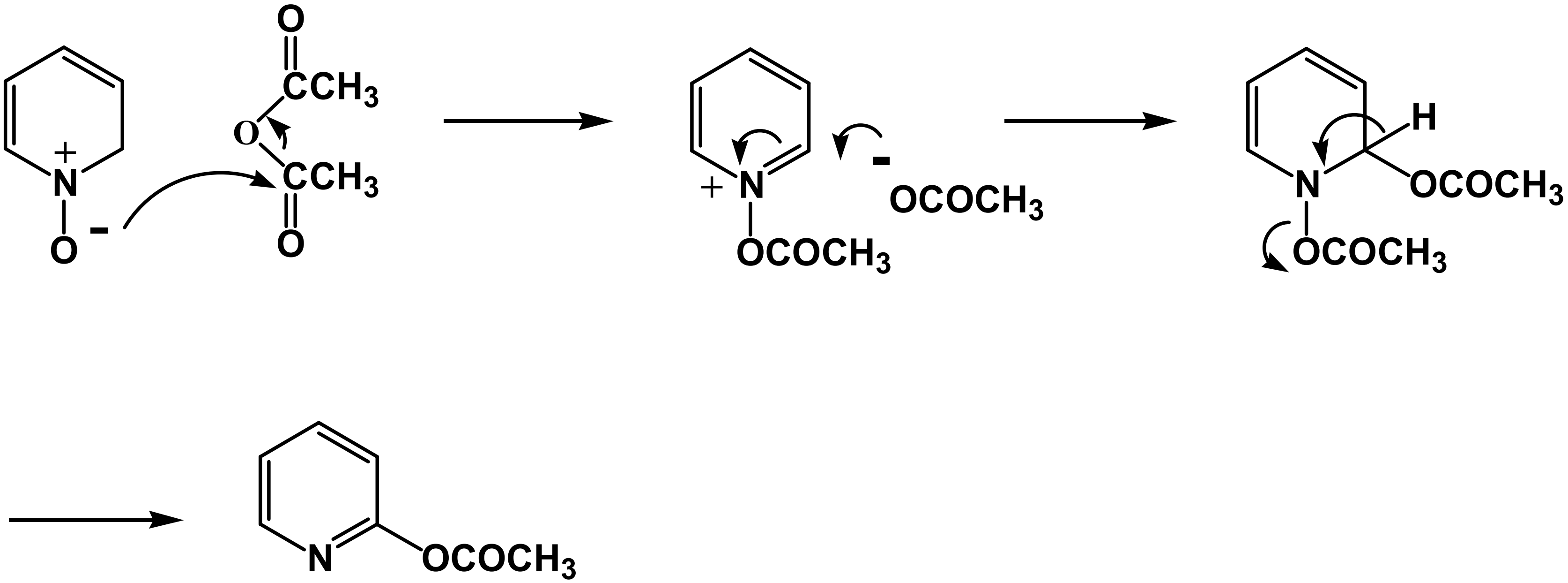


Reazioni elettrofile degli *N*-ossidi di piridina

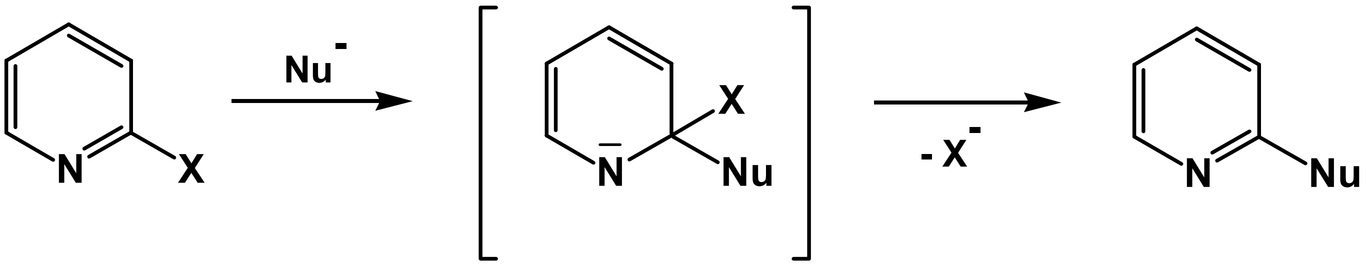


Esercizio: spiegare la reazione

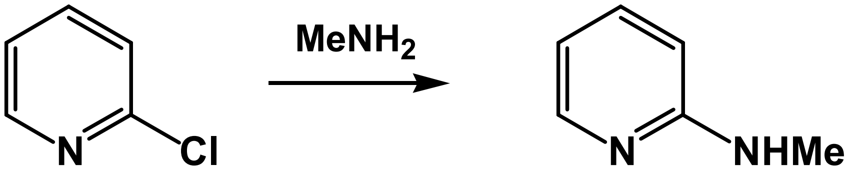


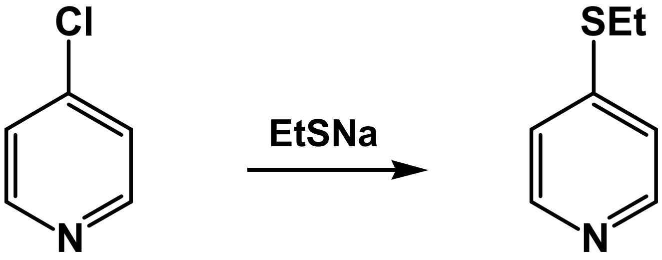


Alogenopiridine: reazioni S_N



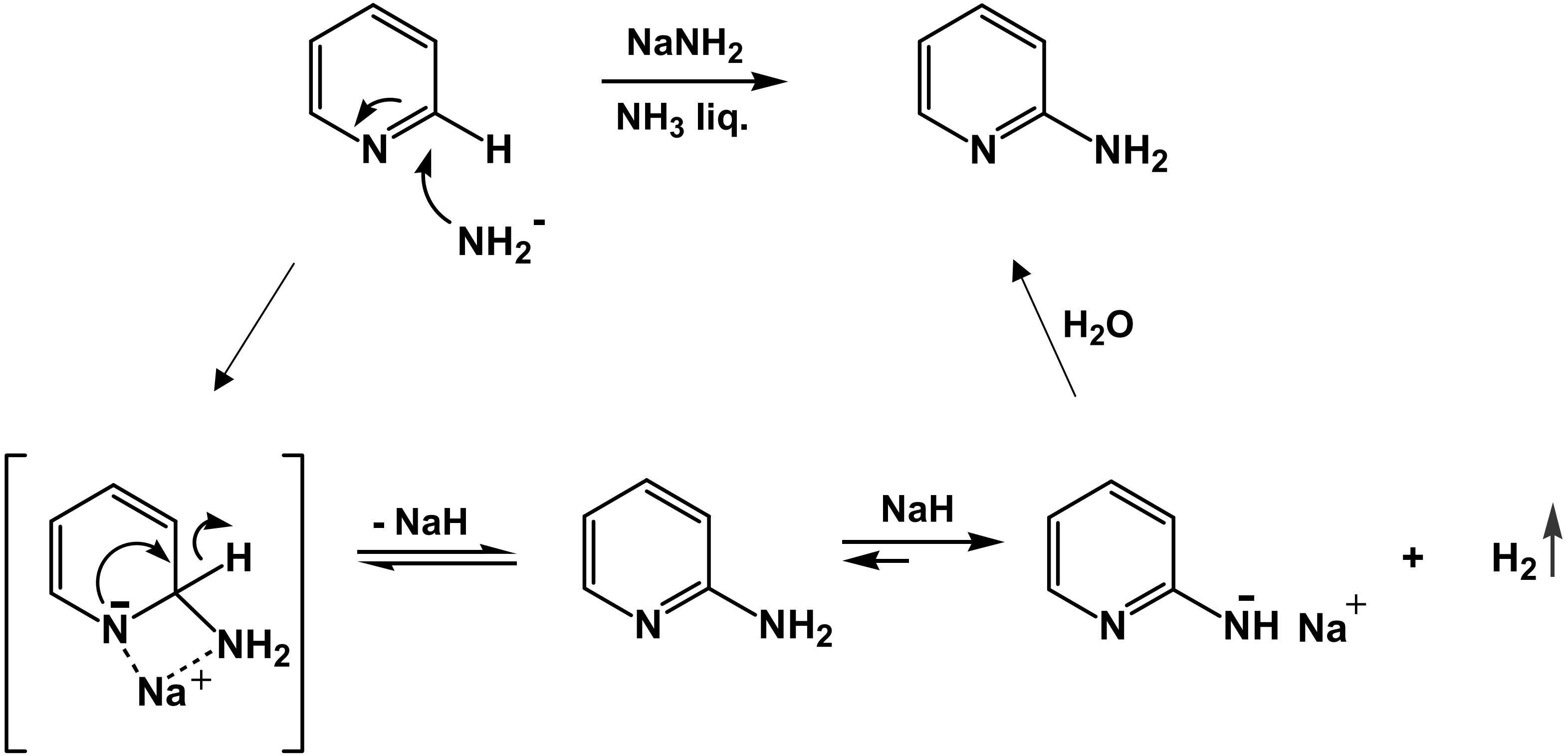
Esempi



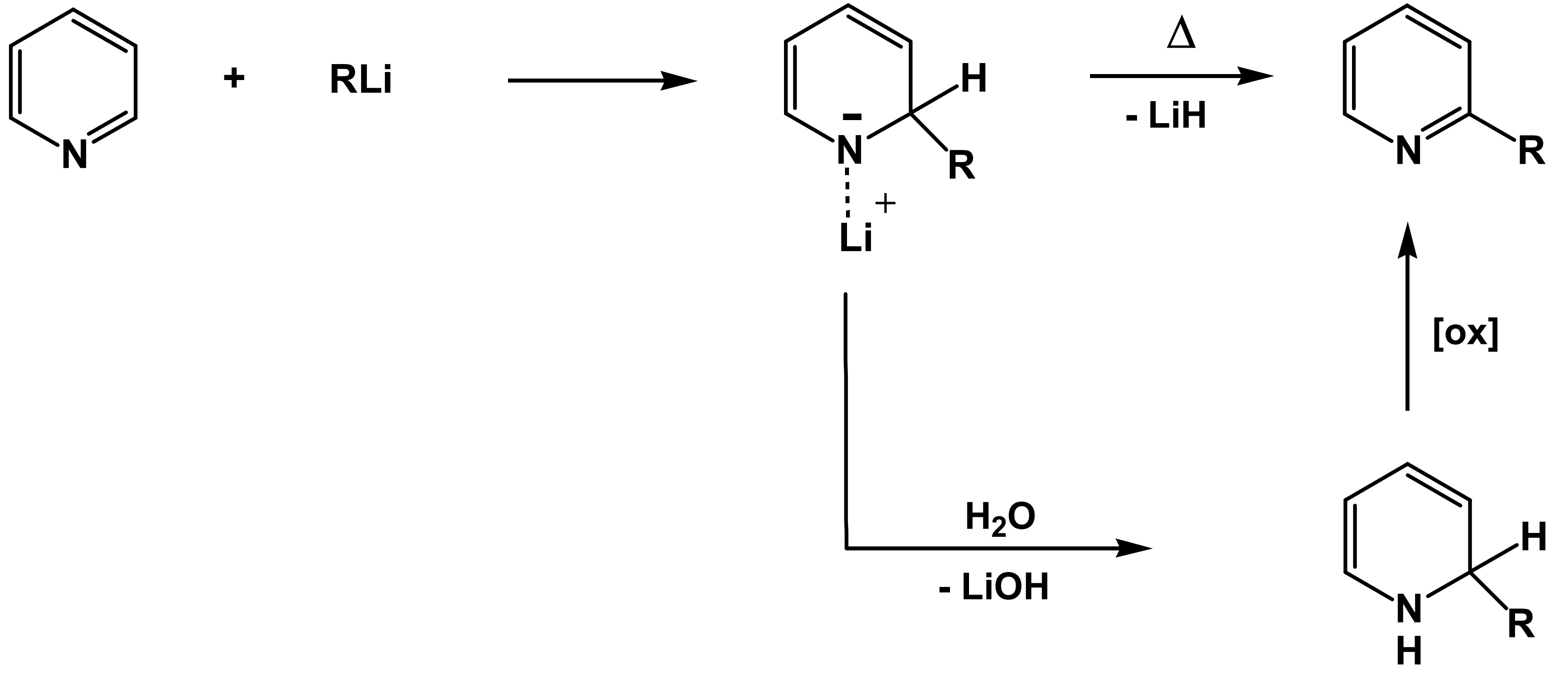


Le 3-alogenopiridine sono poco reattive!

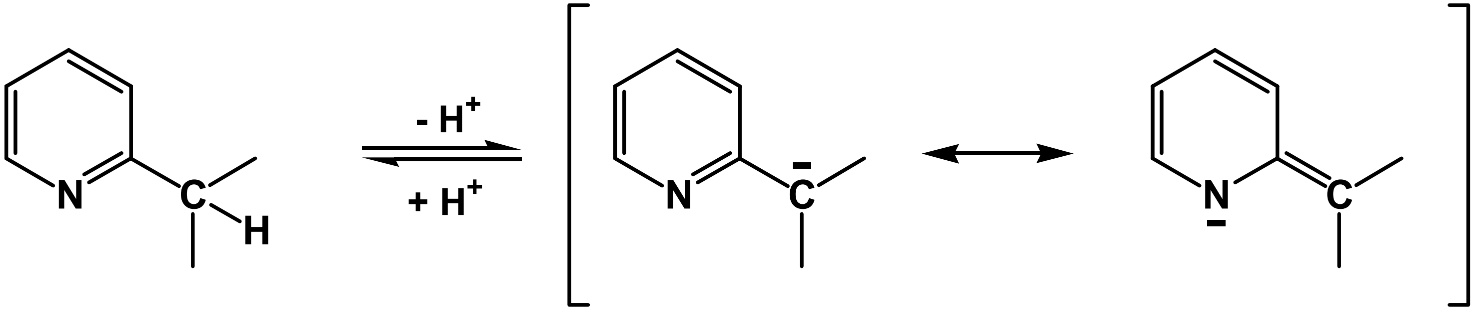
La reazione di Chichibabin

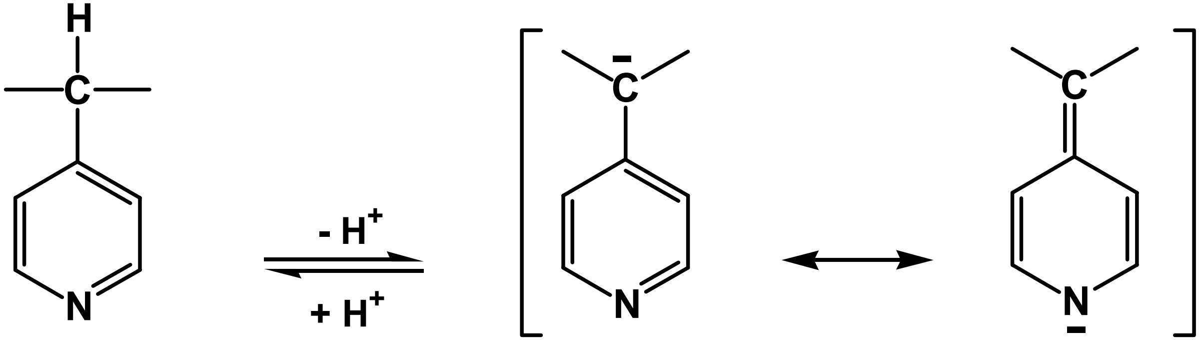


La reazione di Ziegler

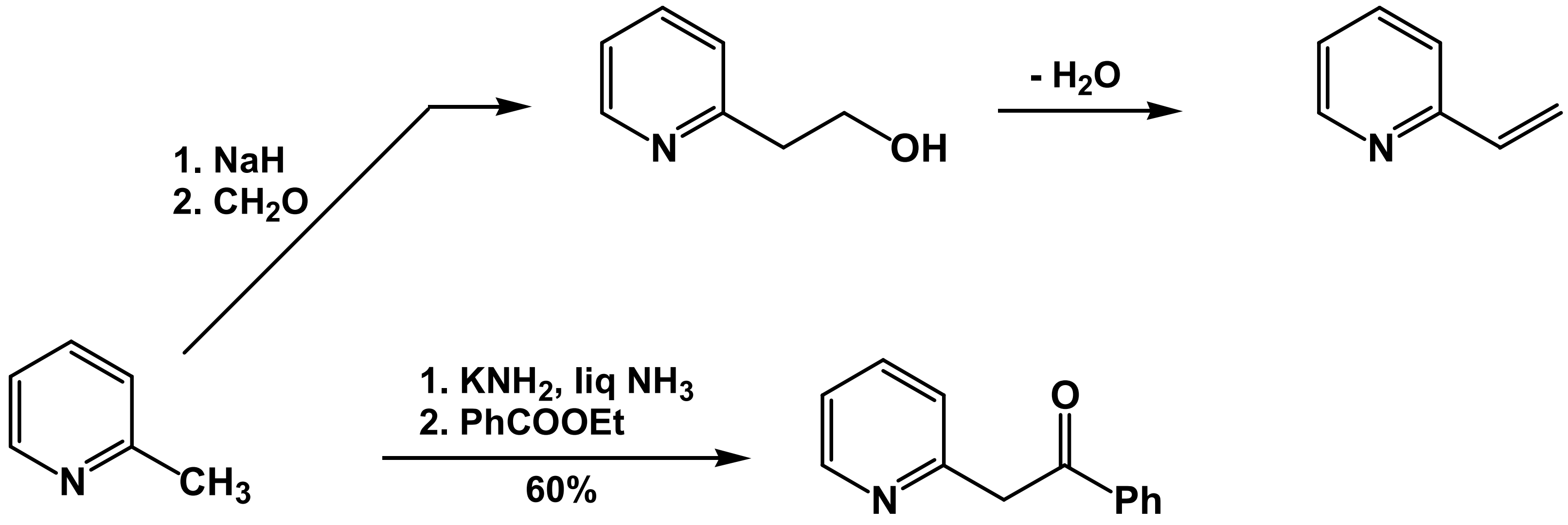


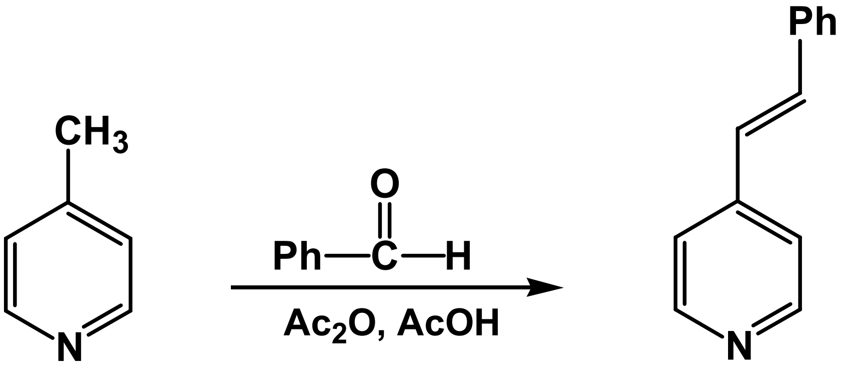
Reattività della catena laterale



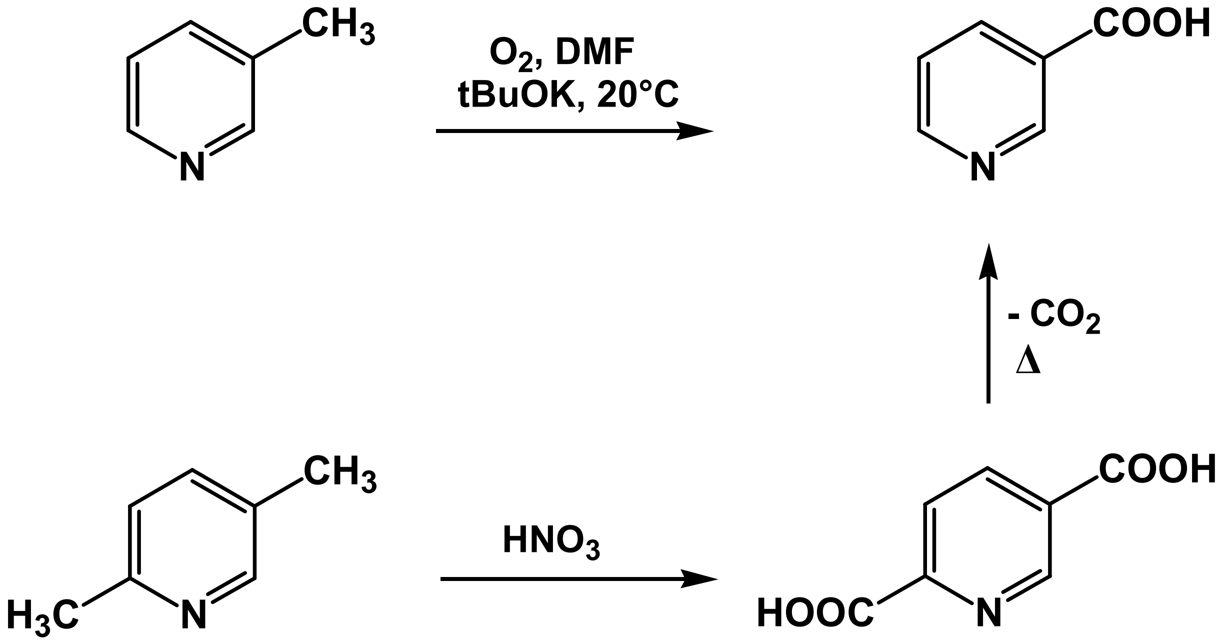


Condensazioni sulla catena laterale

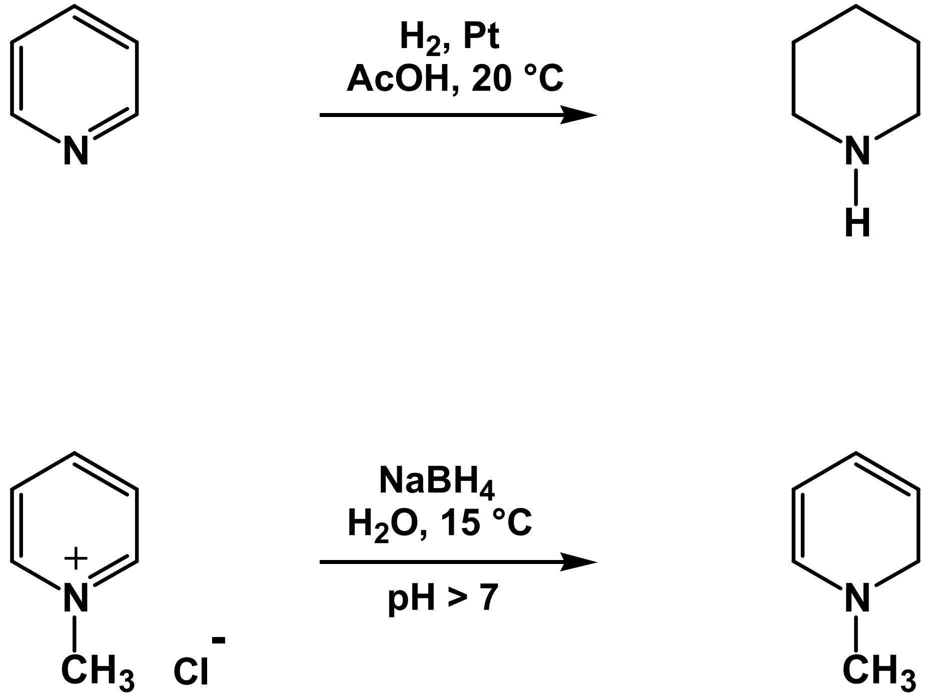




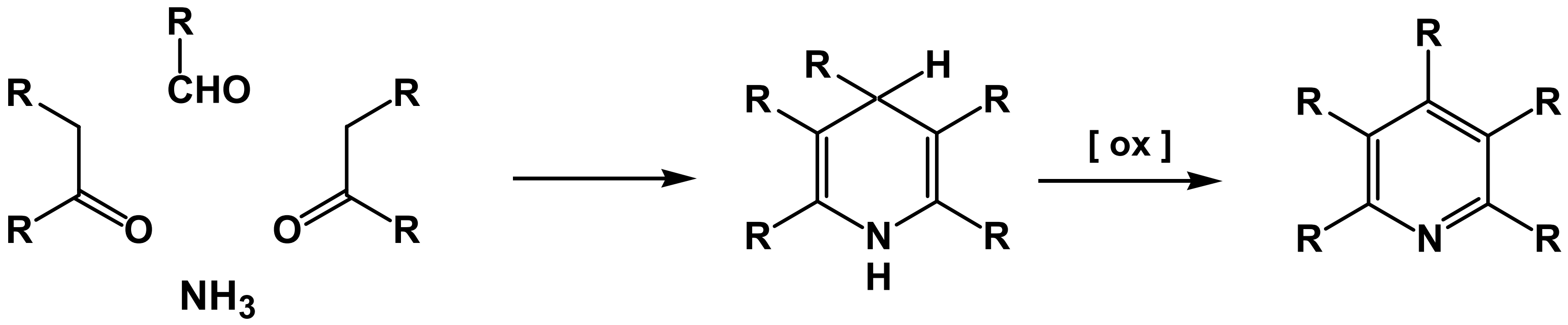
Ossidazione delle piridine



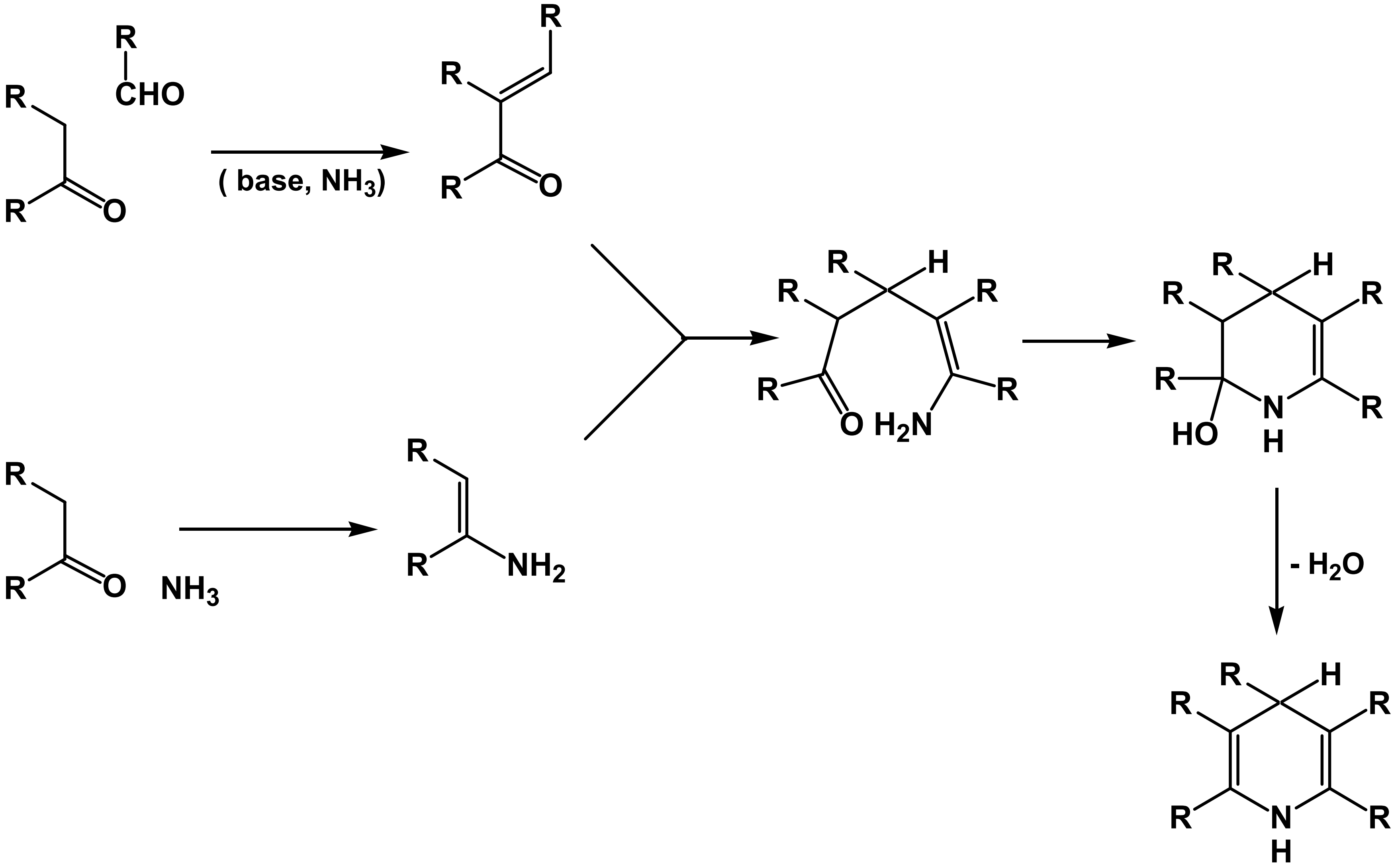
Riduzione delle piridine



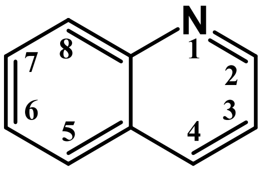
Piridine: sintesi di Hantzsch



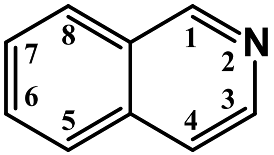
- **Meccanismo**



Chinolina e Isochinolina

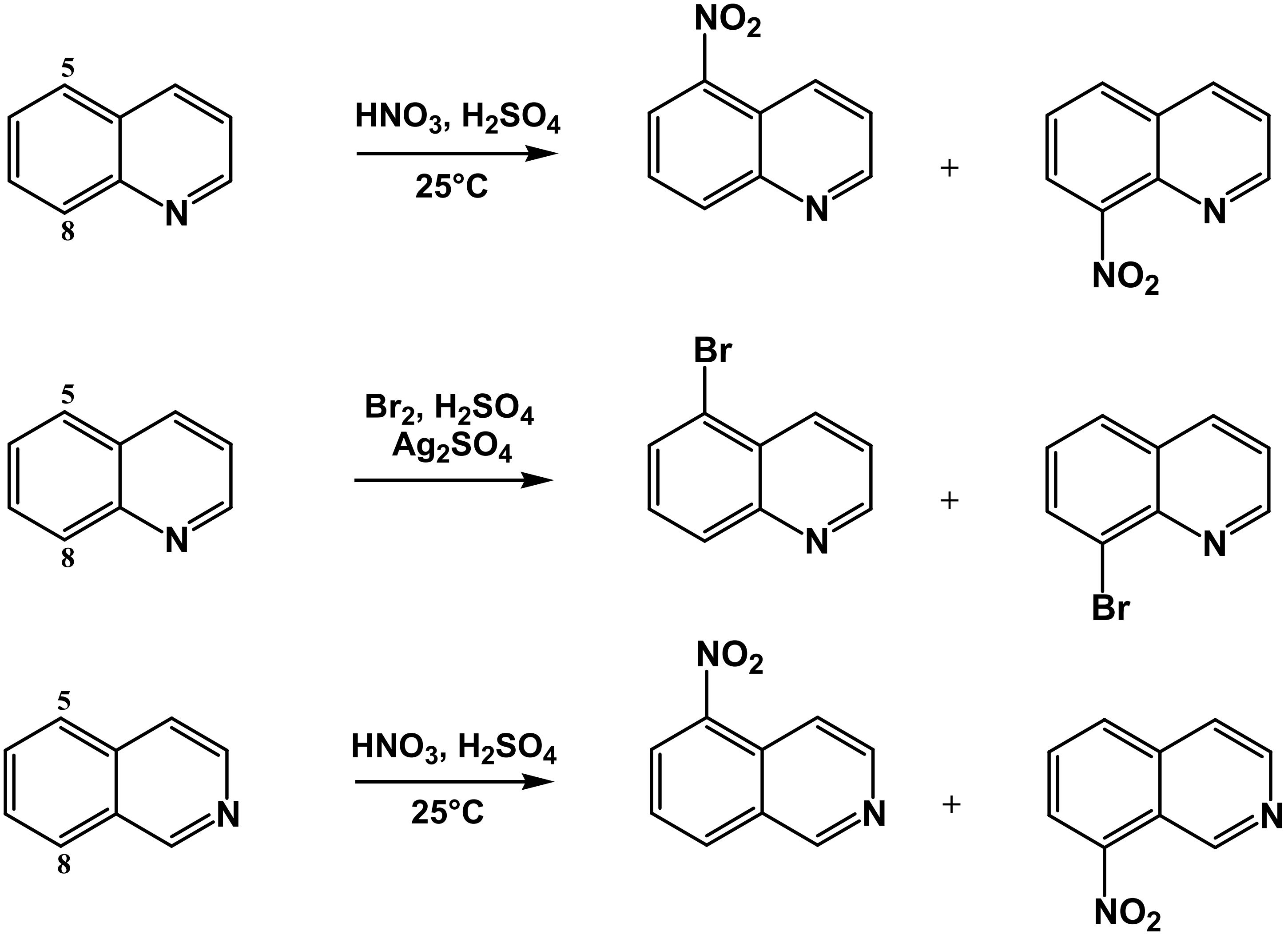


Chinolina

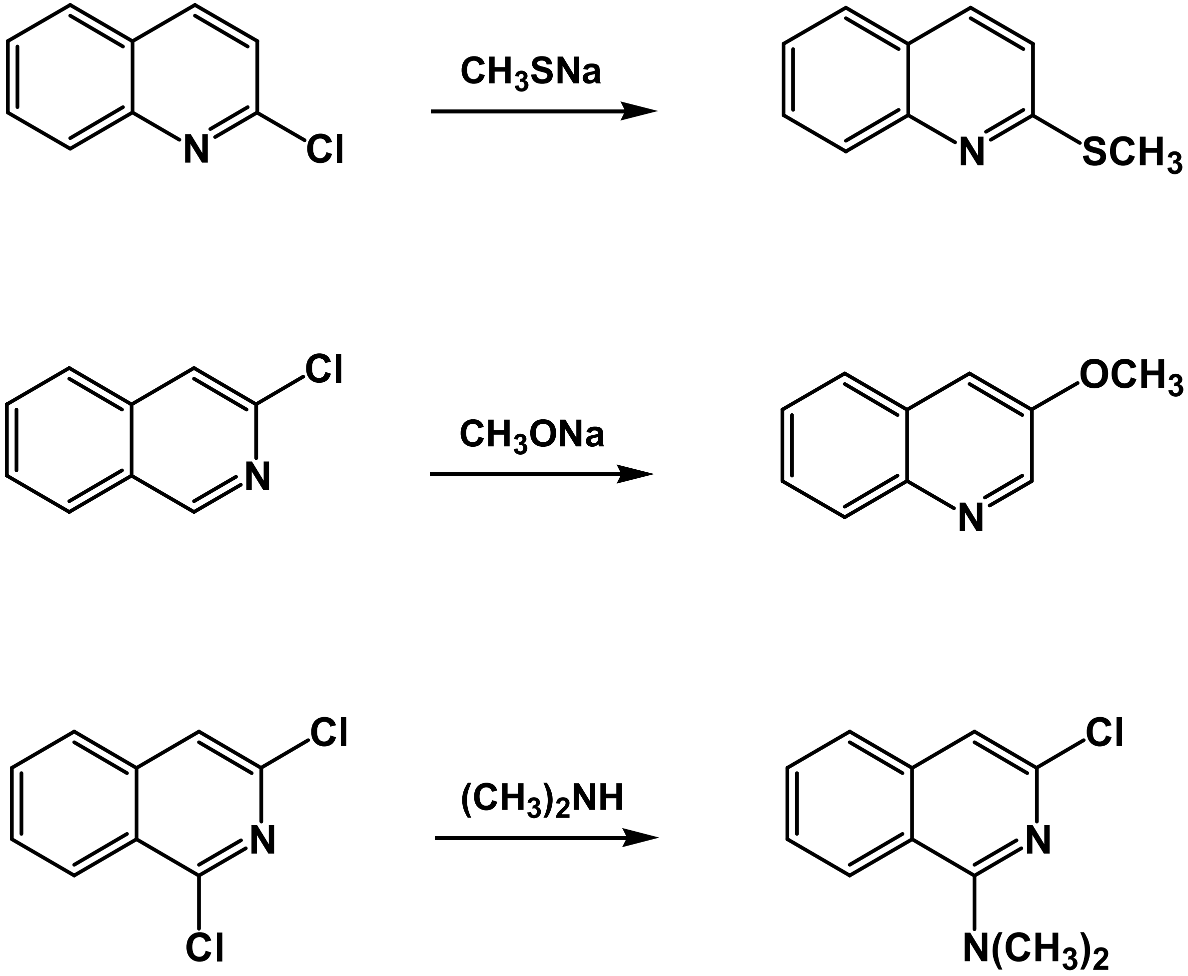


Isochinolina

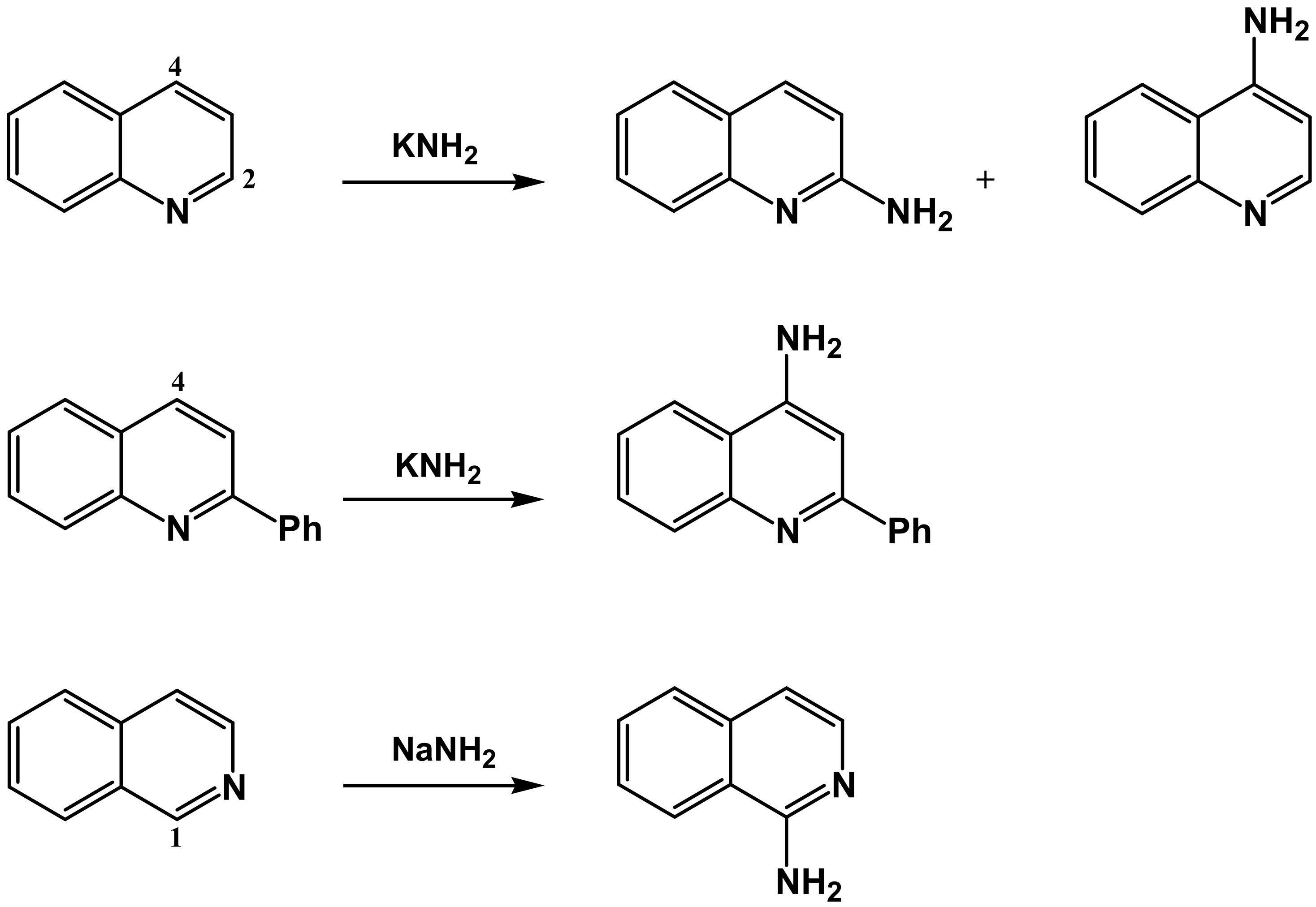
Chinolina e isochinolina: reazioni di sostituzione elettrofila



Chinolina e isochinolina: reazioni S_N

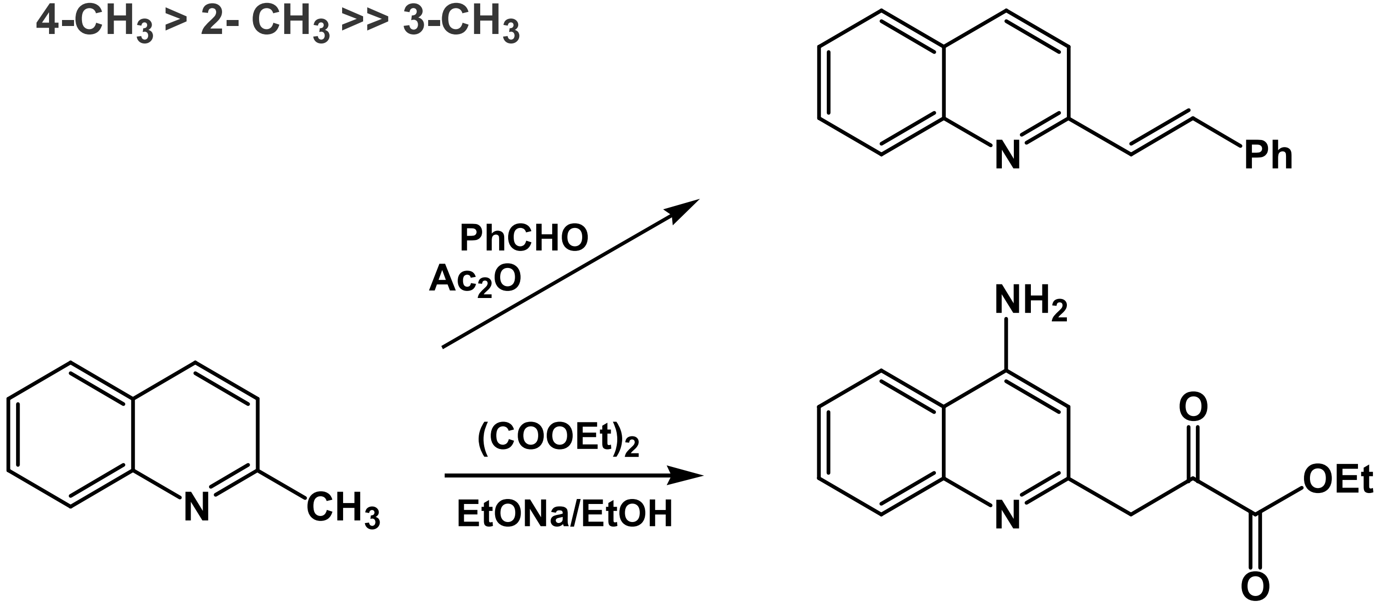


Chinolina e isochinolina: le reazioni di Chichibabin

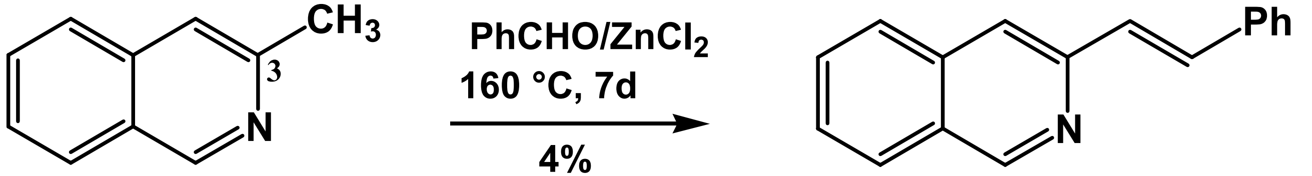


Chinolina e isochinolina: reattività della catena laterale

4-CH_3 > 2- CH_3 >> 3-CH_3

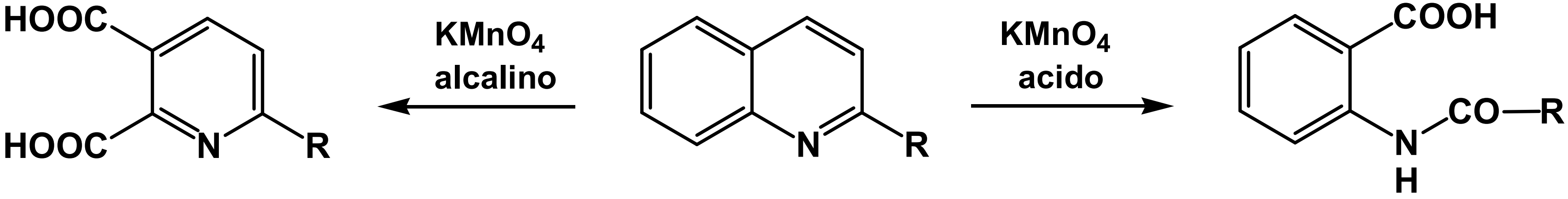


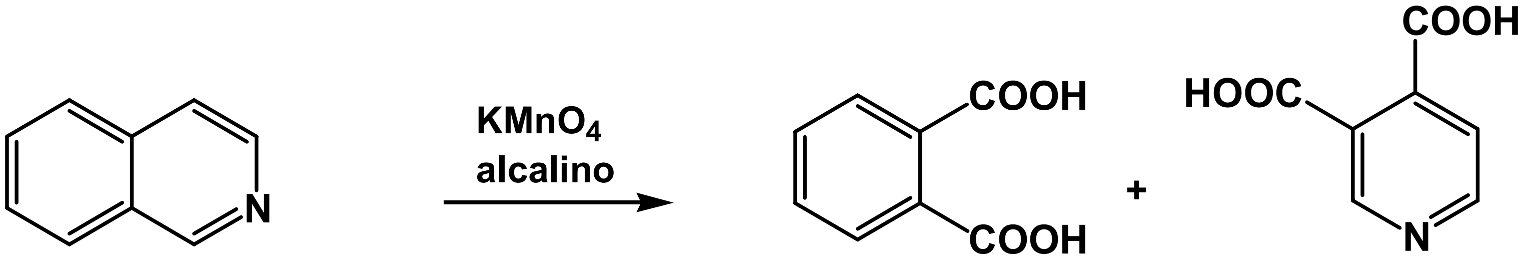
1-CH_3 >> 3-CH_3

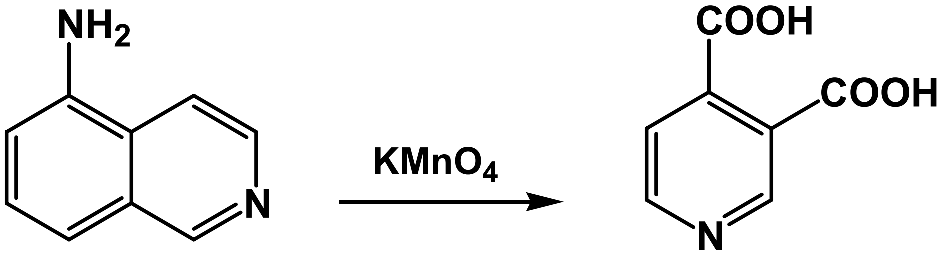


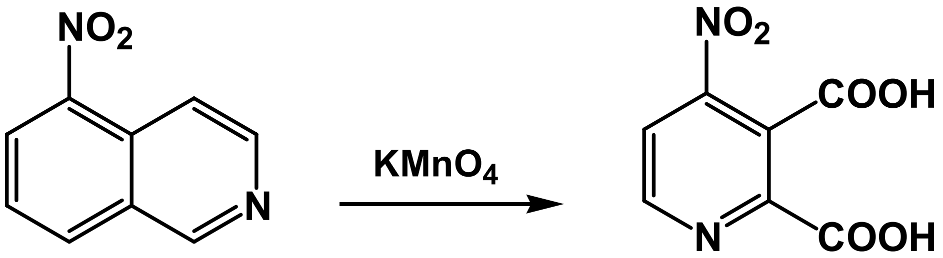
Chinolina e isochinolina: ossidazione

controlla

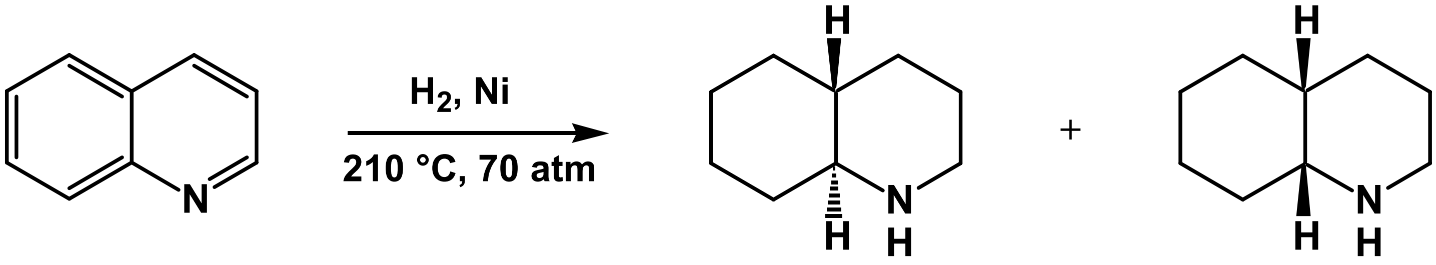


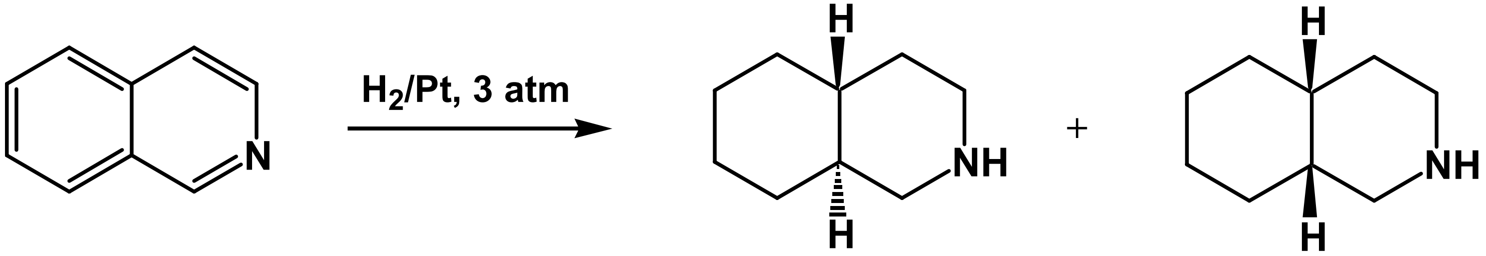



NH2
N
KMnO4
COOH
COOH
N

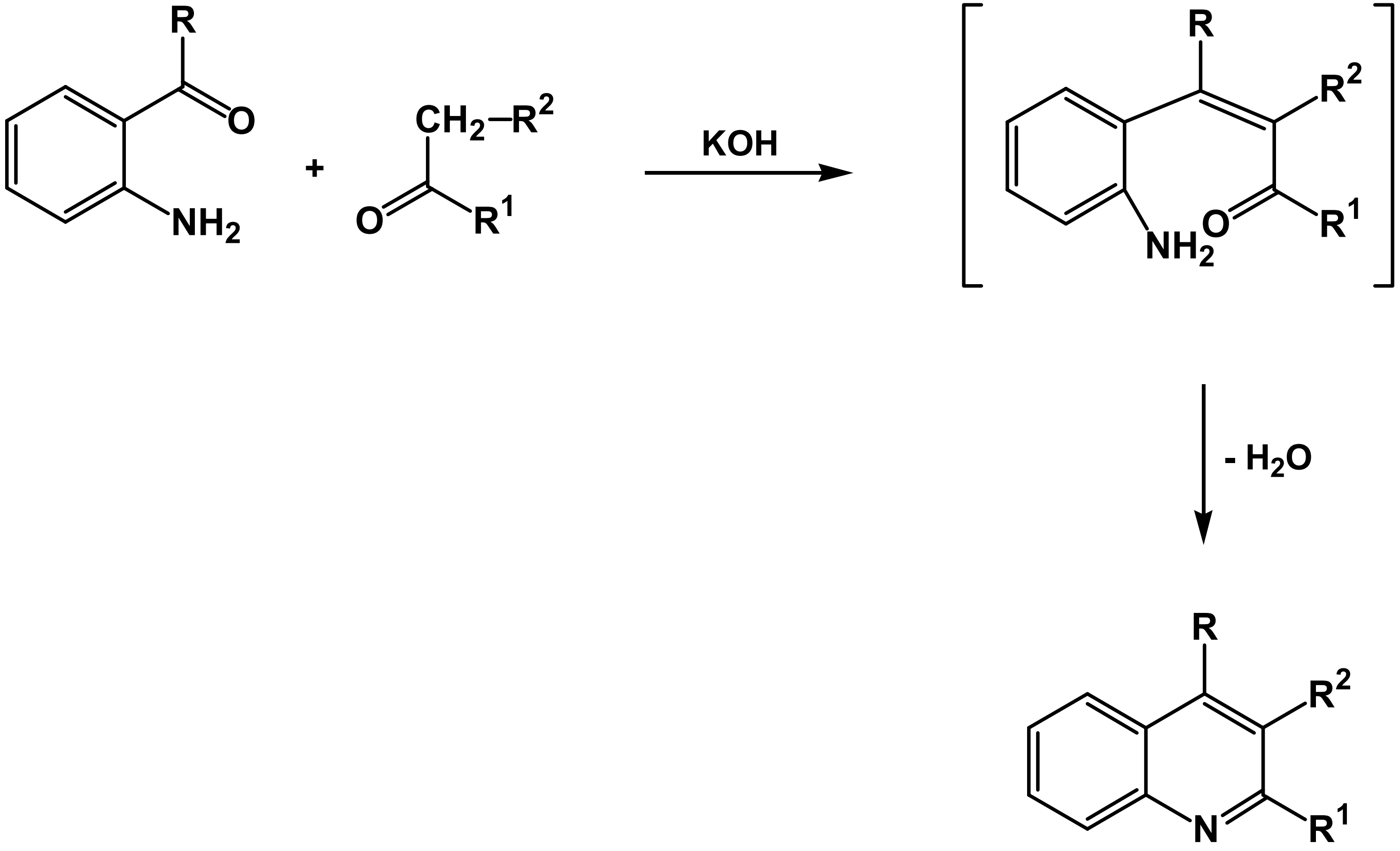

NO2
N
KMnO4
NO2
COOH
N
COOH

Chinolina e isochinolina: riduzione

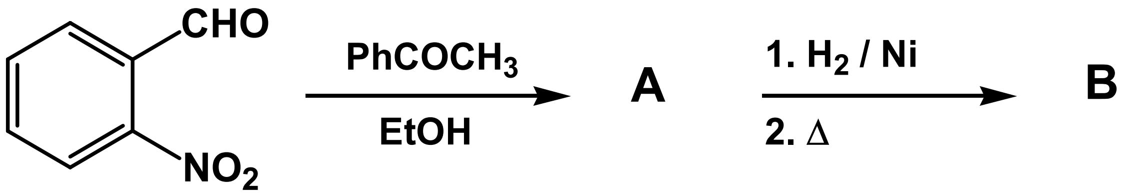




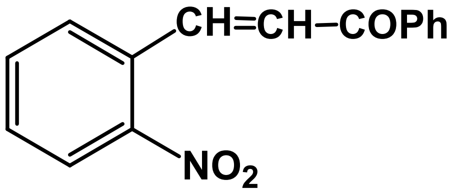
Chinolina: sintesi di Friedländer



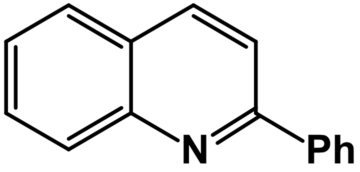
Esercizio: quale derivato chinolinico B si ottiene?



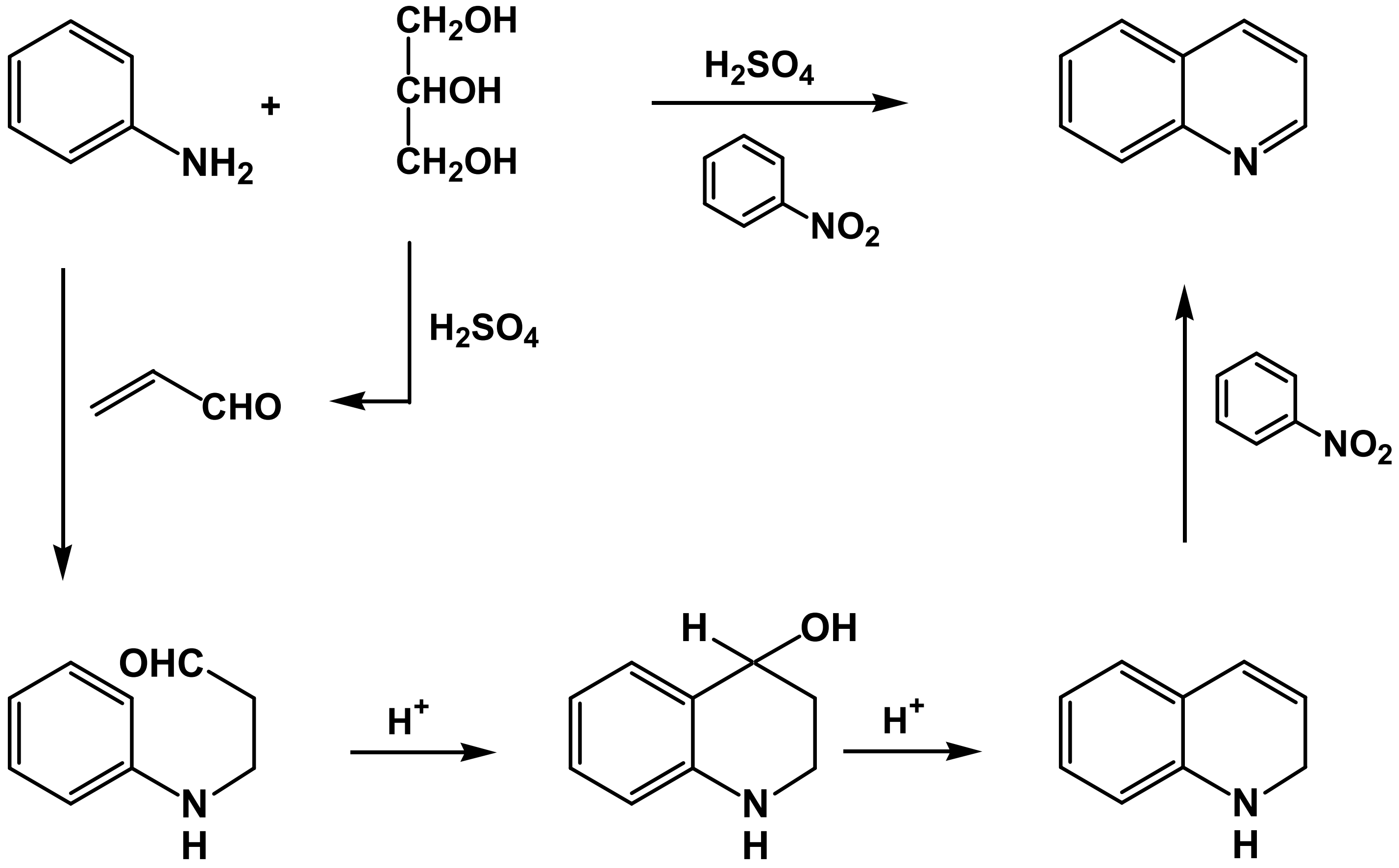
A =



B =



Chinolina: sintesi di Skraup

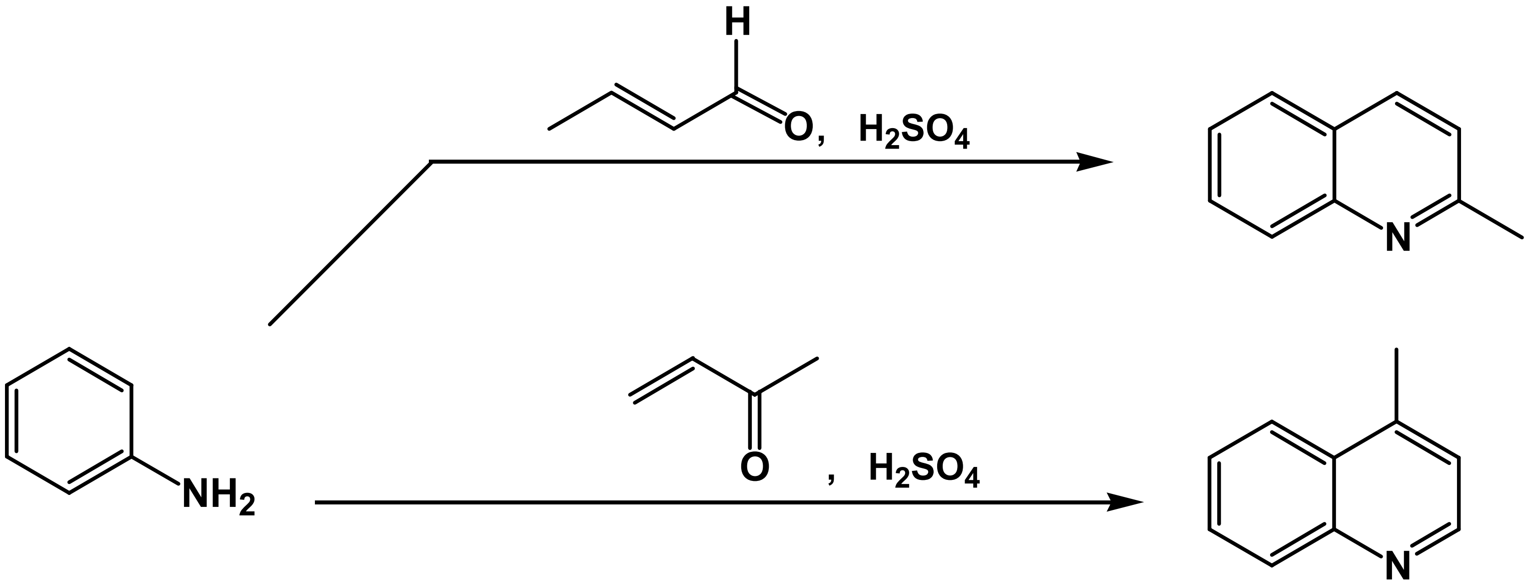


Zdenko Hans SKRAUP

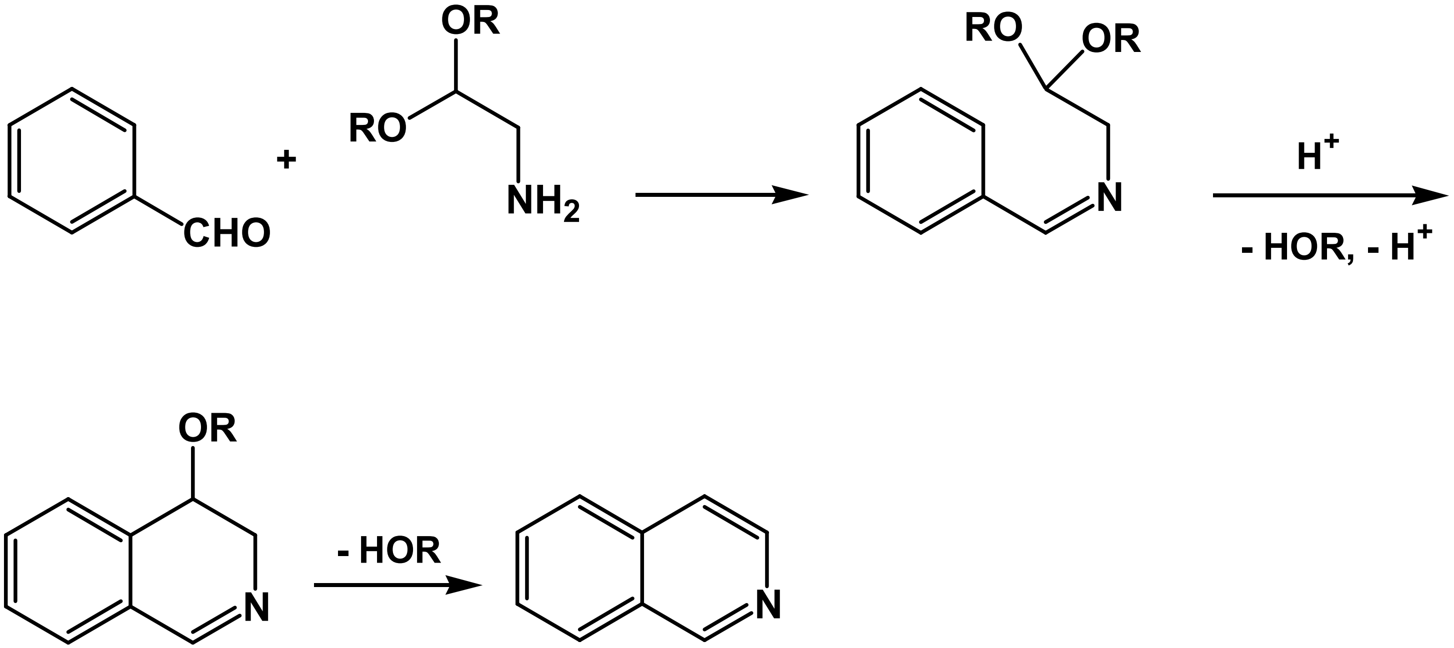
- Nato a Praga nel 1850 e morto a Vienna nel 1910, si occupò soprattutto di chimica organica, soprattutto carboidrati e alcaloidi. Nel 1880 pubblicò in Monatshefte für Chemie [**1**, 316 (1880)] la sintesi della chinolina che porta il suo nome. Si occupò anche di analisi capillare, tecnica che precede la cromatografia su carta. Fu professore a Graz e Vienna.

Chinoline: sintesi di Doebner-Miller

Il meccanismo è lo stesso della sintesi di Skraup; originalmente il nome era limitato alla reazione con l'aldeide crotonica.

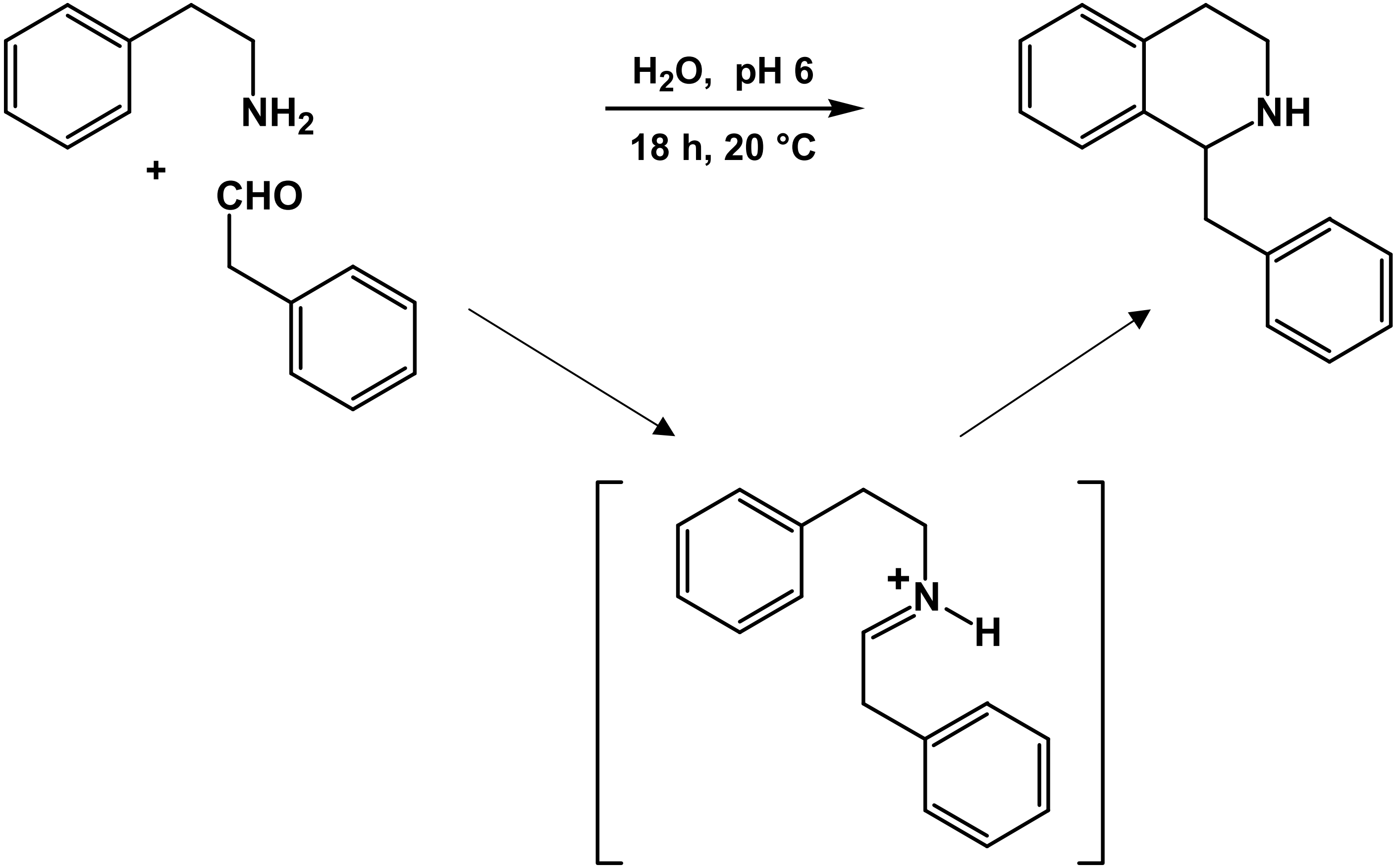


Isochinoline: sintesi di Pomeranz-Fritsch

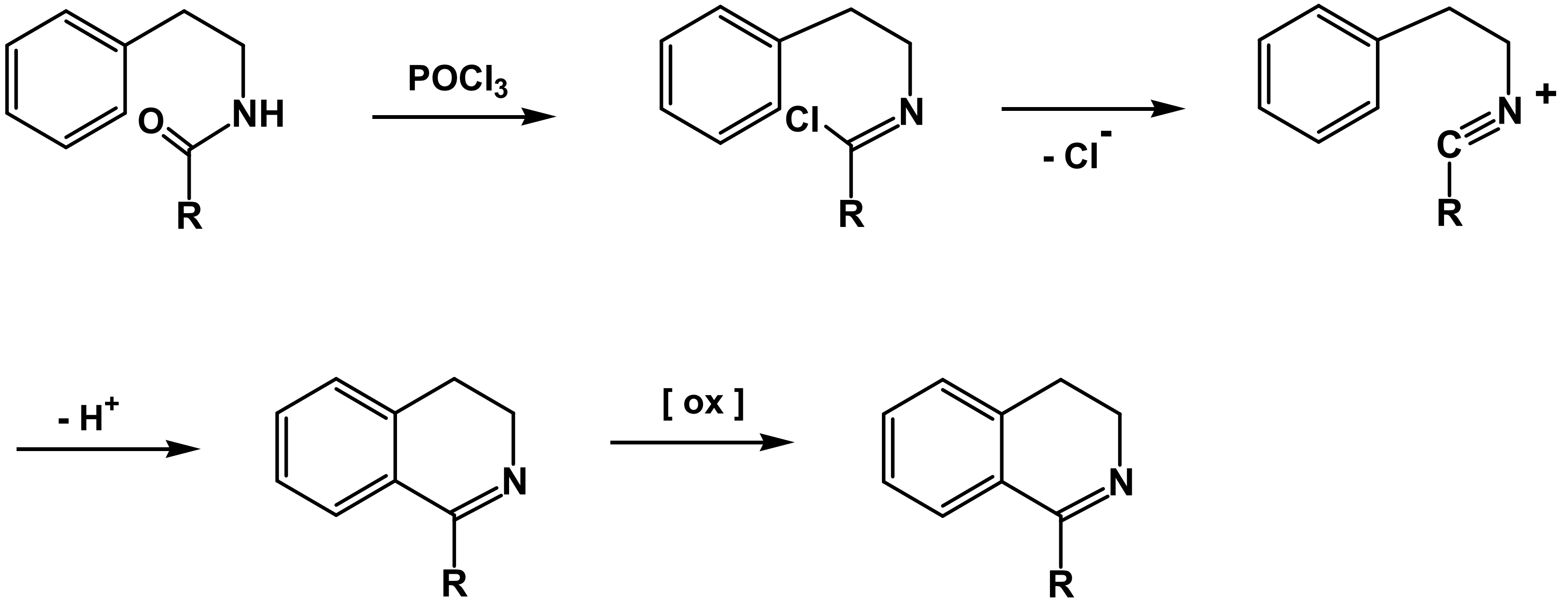


Isochinoline: sintesi di Pictet-Spengler

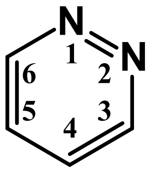
Sintesi in condizioni biomimetiche



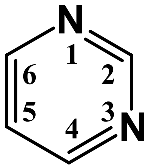
Isochinoline: sintesi di Bischler-Napieralsky



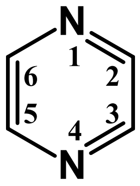
Le diazine



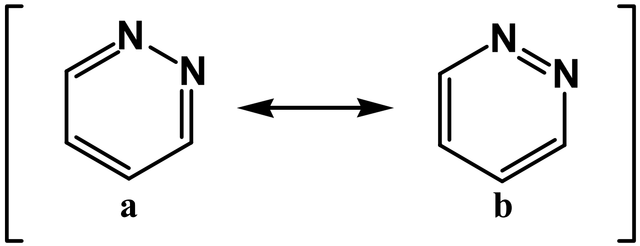
Piridazina (1,2-diazina)



Pirimidina (1,3-diazina)

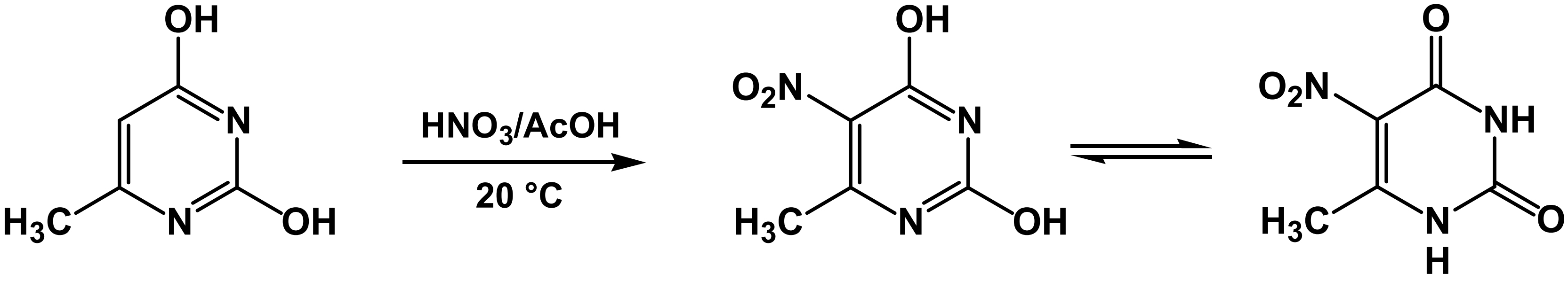


Pirazina (1,4-diazina)

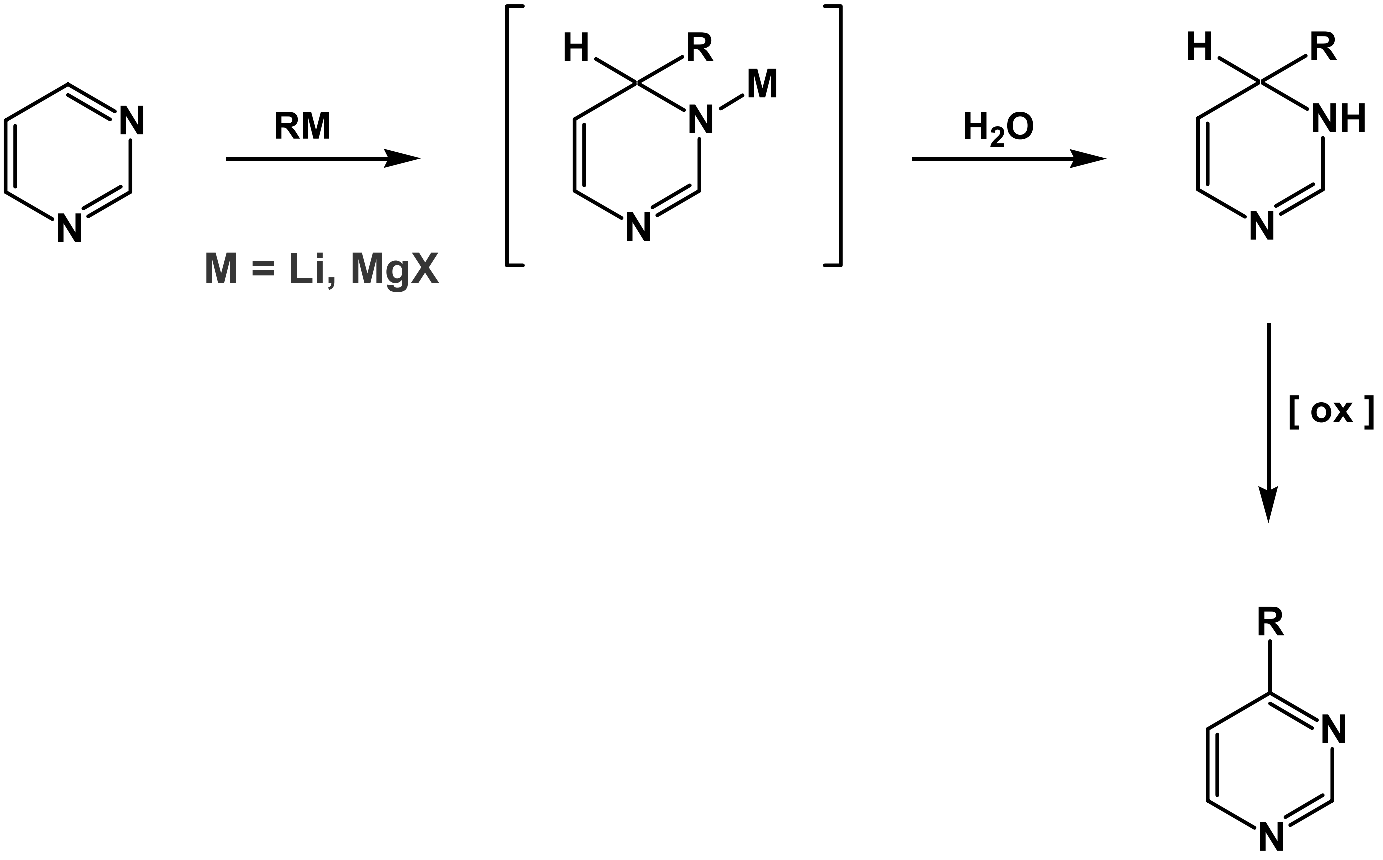


Diazine

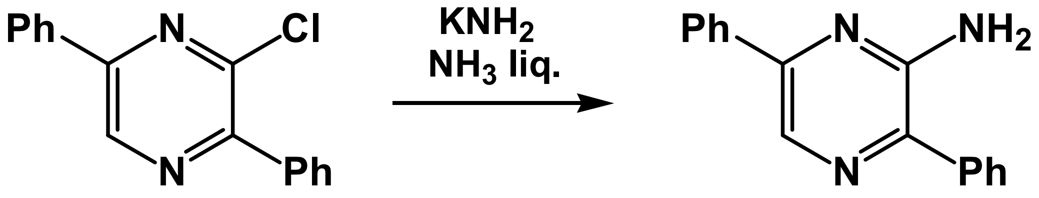
Le *sostituzioni elettrofile* sono possibili solo sui composti attivati!

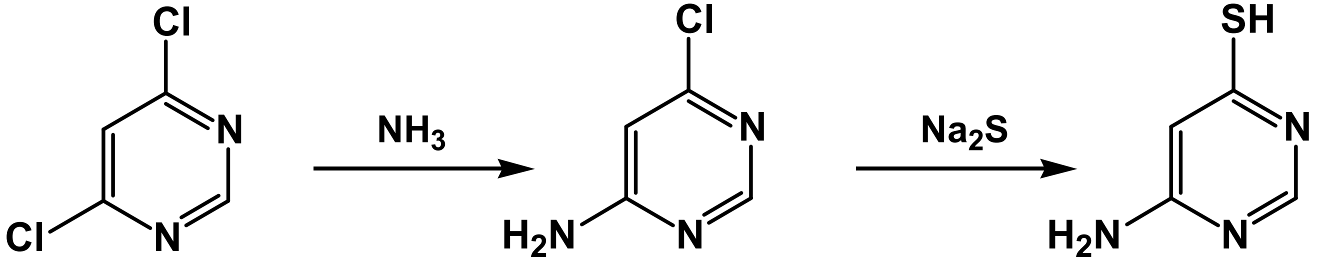


Diazine: reazioni con composti organometallici

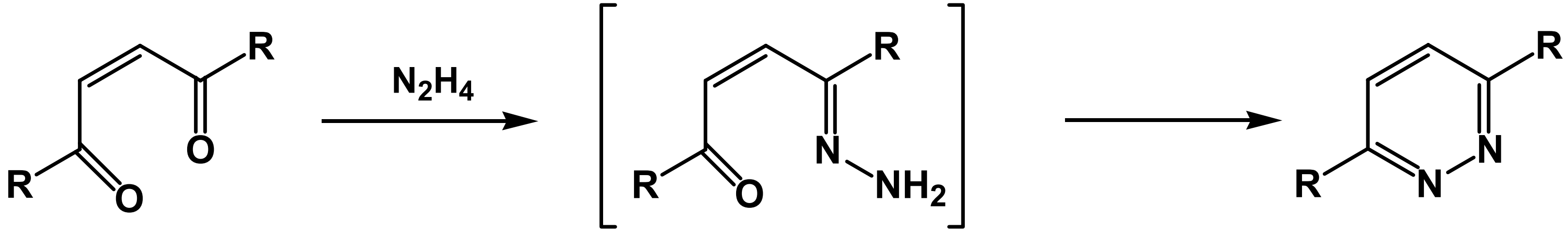


Diazine: sostituzioni nucleofile

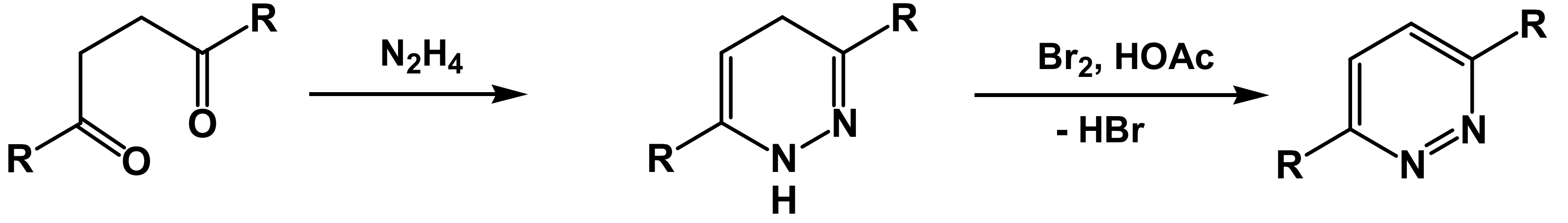




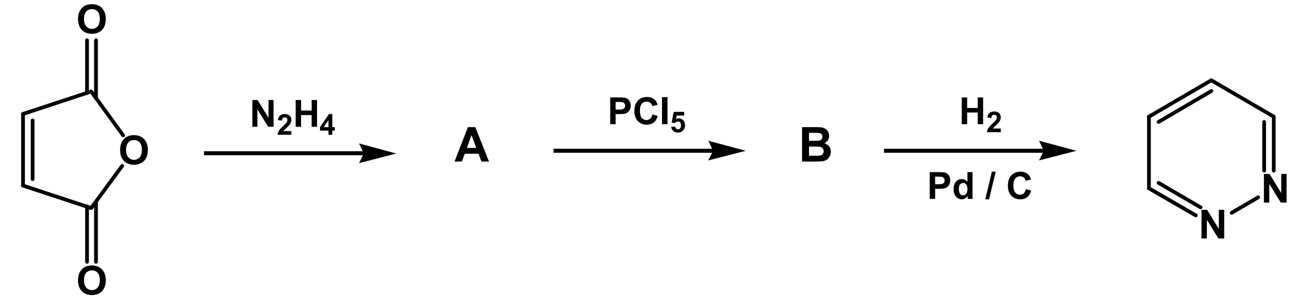
Sintesi della piridazina



oppure

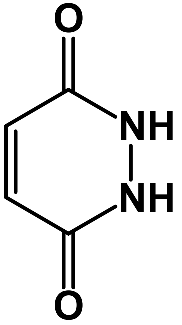


Esercizio: la piridazina non sostituita si può ottenere con le seguenti reazioni

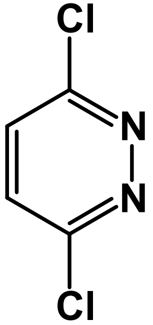


Indicare **A** e **B**

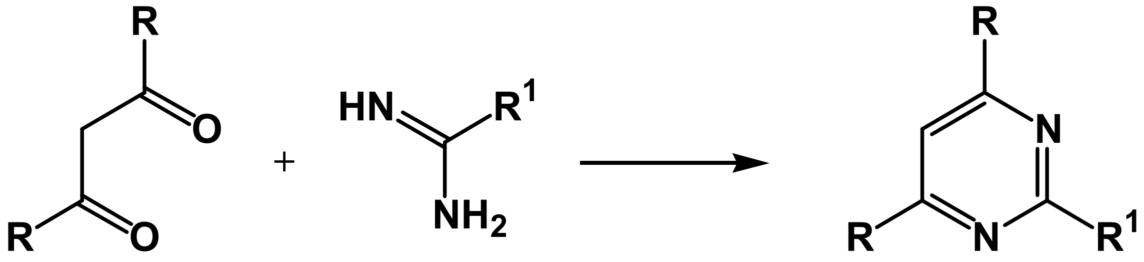
A =

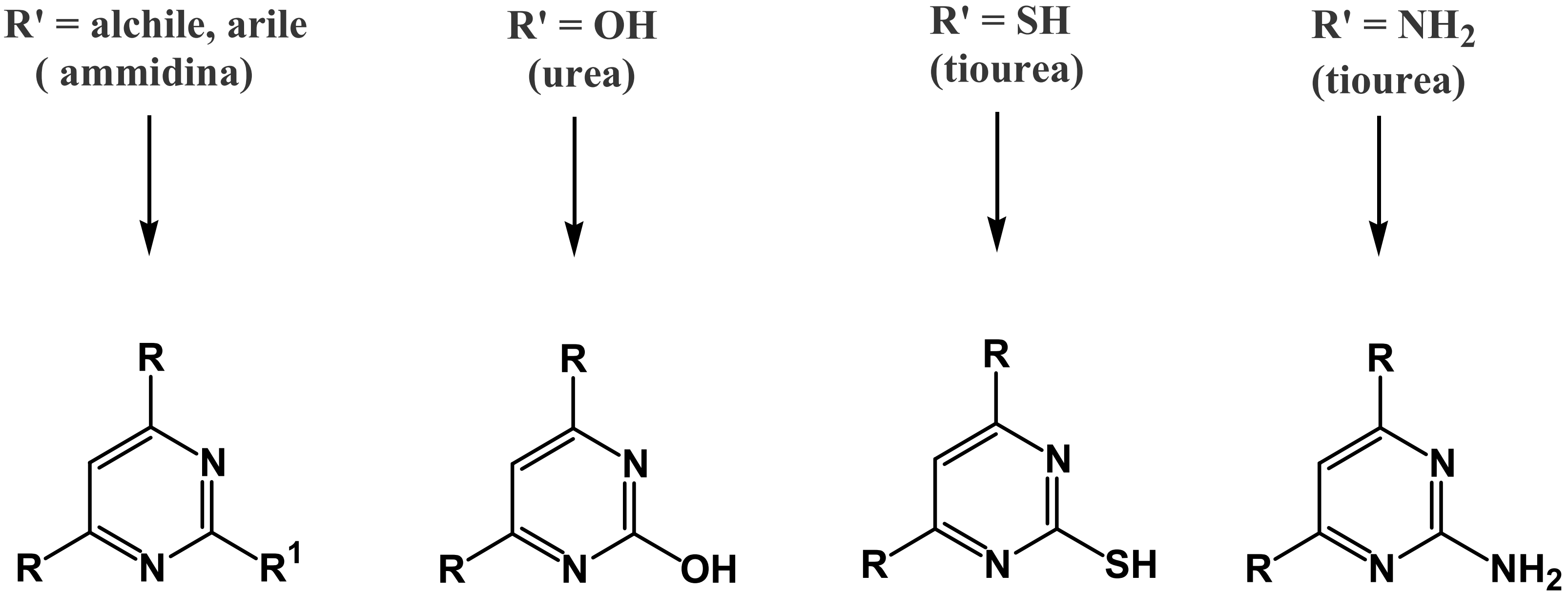


B =



Pirimidina: sintesi




R' = alchile, arile
(ammidina)

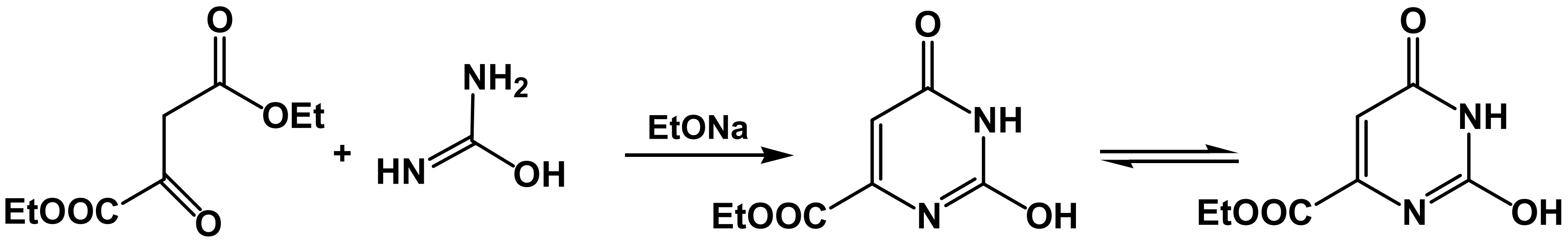
R' = OH
(urea)

R' = SH
(tiourea)

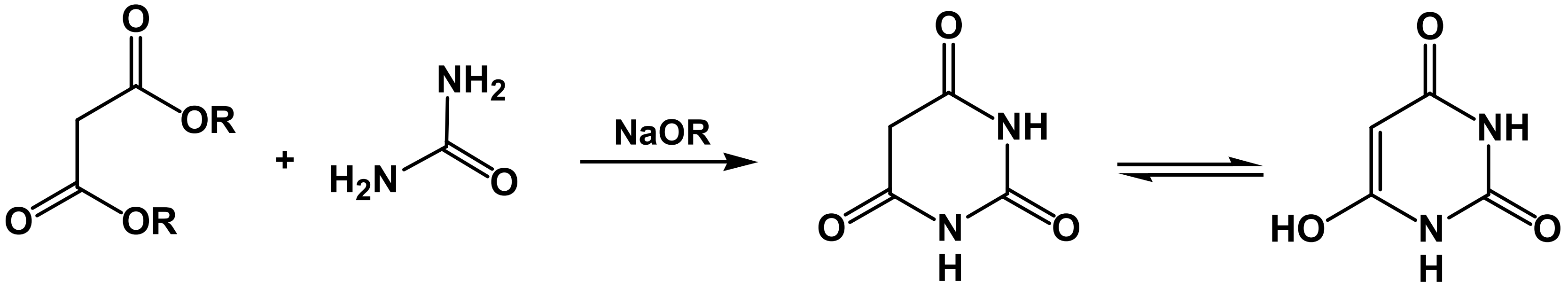
R' = NH_2
(tiourea)

Alcuni derivati pirimidinici importanti

Acido orotico



Acido barbiturico



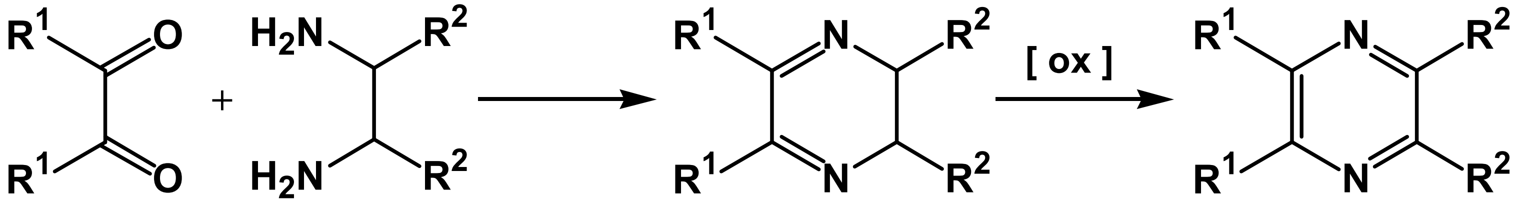
La storia della scoperta dell'acido barbiturico è una storia classica.

Si racconta che nel giorno di Santa Barbara del 1864 un gruppo di artiglieri stava festeggiando la loro patrona in una taverna. Il chimico tedesco Adolph von Baeyer (fondatore dell' industria chimica Bayer e vincitore del Premio Nobel nel 1905), che aveva appena sintetizzato la cosidetta "malonilurea" dall'acido malonico e dall'urea, capitò nello stesso locale e si unì al gruppo. Qui la storia si fa confusa a causa della grande quantità di birra. Sta di fatto che l'allegra compagnia uscì dalla taverna dopo aver battezzato il nuovo composto chimico con il nome di acido barbiturico combinando i nomi dell'acido malonico, dell'urea e di Santa Barbara!

Adolph von Baeyer

Santa Barbara

Sintesi della pirazina



oppure