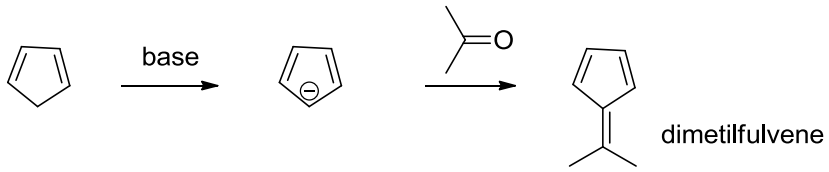
Oltre la metà dei composti organici conosciuti sono eterocicli aromatici

Eterocicli aromatici sono:

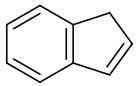
molti principi attivi farmaceutici
composti di interesse agrochimico
profumi
coloranti
aromi alimentari

Orbitali Molecolari nei composti aromatici
circonferenze di Frost e regola di Huckel

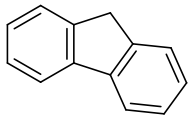
il ciclopentadienil anione
ha caratteristiche
aromatiche



dimetilfulvene



indene



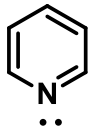
fluorene

Indene e Fluorene
correlati al ciclopentadiene
mostrano simile reattività

Orbitali Molecolari nei composti aromatici

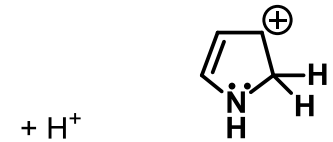
Circonferenze di **Frost** e regola di **Huckel**

PIRROLO (isoelettronico al ciclopentadienilanione)
coppia di elettroni in orbitale p
partecipa all'aromaticità



PIRIDINA
coppia di elettroni in orbitale sp2
non partecipa ad aromaticità

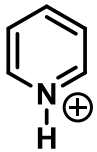
Pirrolo



PIRROLIO
pKa - 4

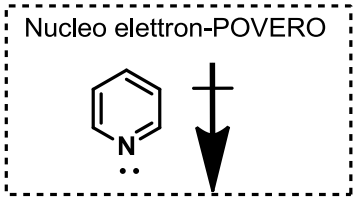
Il pirrolo non ha caratteristiche di base

Piridina

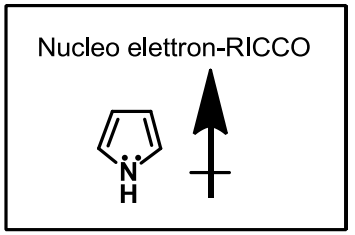


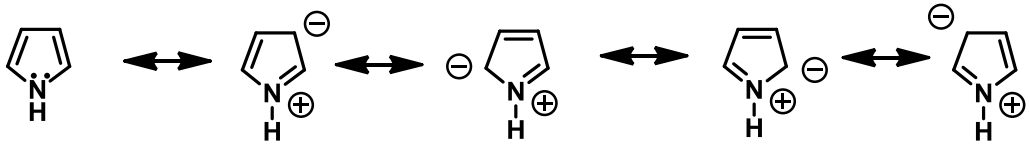
PIRIDINIO
pKa 5,5

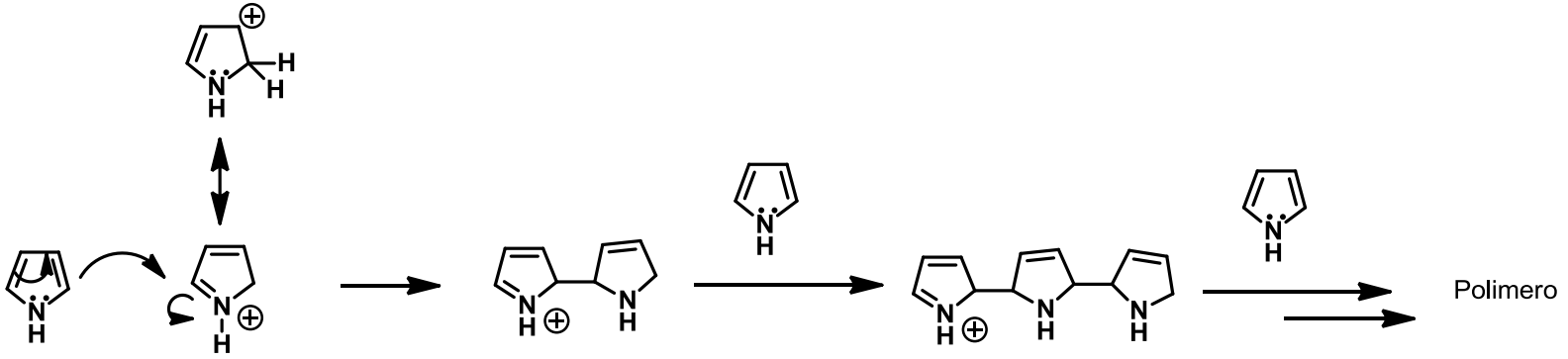
La piridina è una base di forza moderata

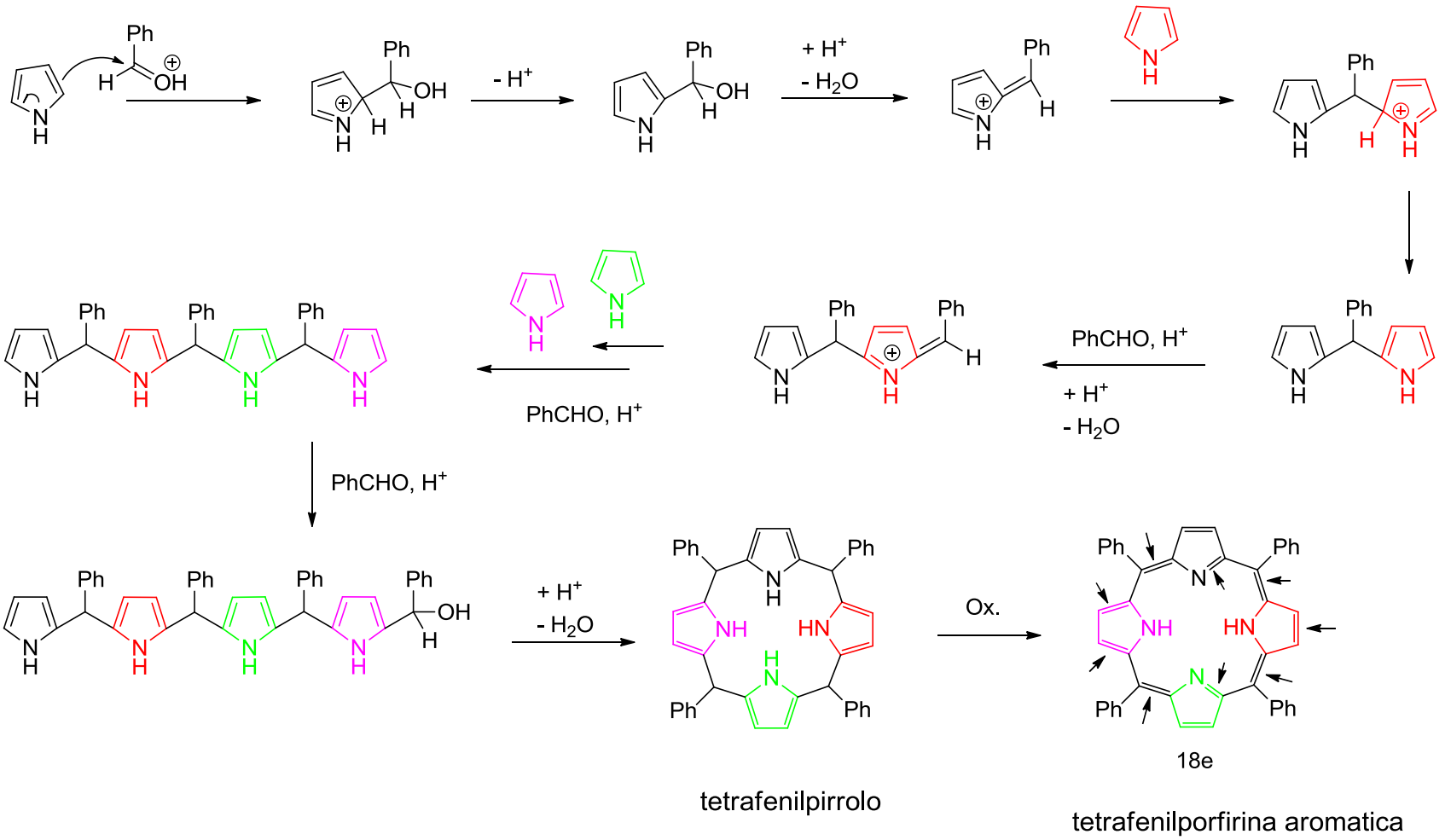


composti eterociclici pentaatomici
reagiscono **troppo facilmente**
con elettrofili e sono instabili
in ambiente acido (Bronsted o Lewis)



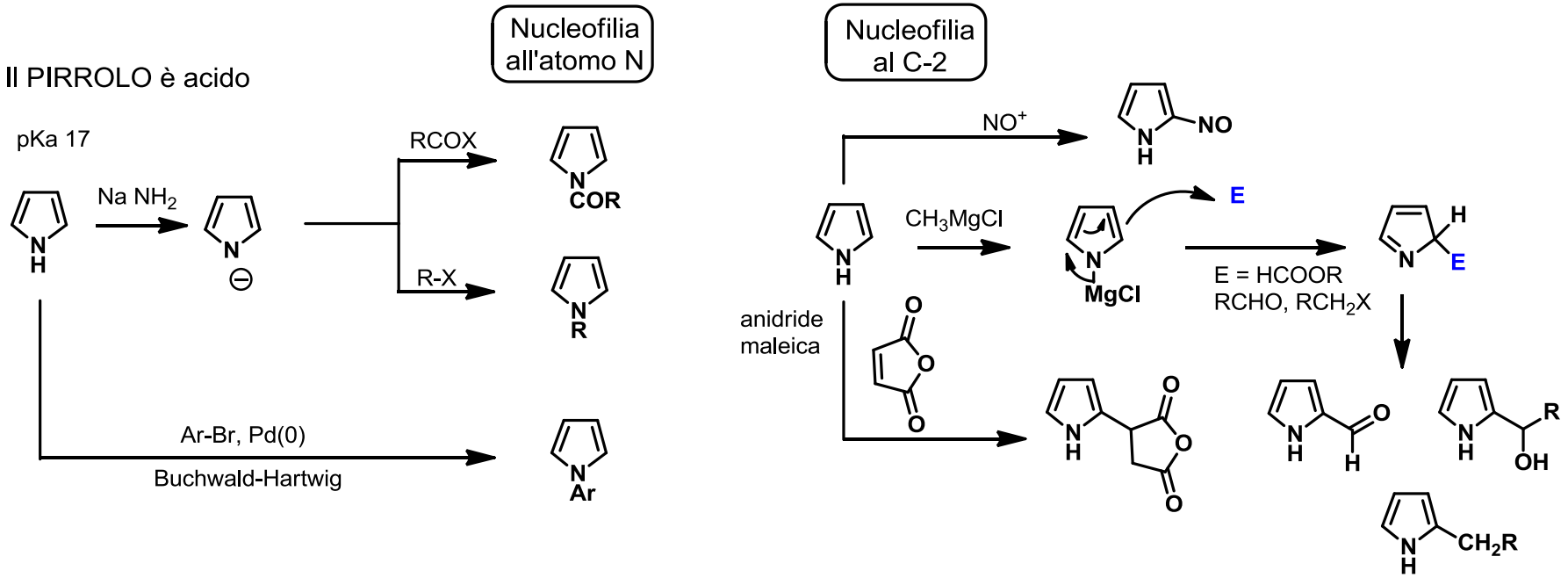




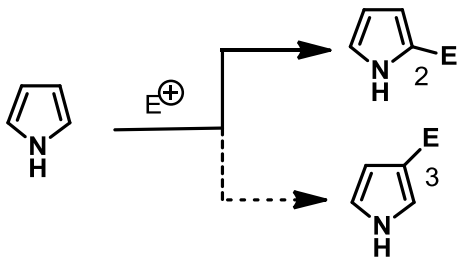


tetrafenilpirrolo

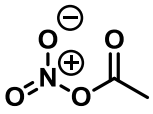
tetrafenilporfirina aromatica


Il PIRROLO è acido
pKa 17
Na NH2
RCOX
R-X
Ar-Br, Pd(0)
Buchwald-Hartwig
Nucleofilia all'atomo N
Nucleofilia al C-2
NO+
CH3MgCl
MgCl
E
E = HCOOR
RCHO, RCH2X
anidride maleica

Nucleofilia al C-2



ELETTROFILI



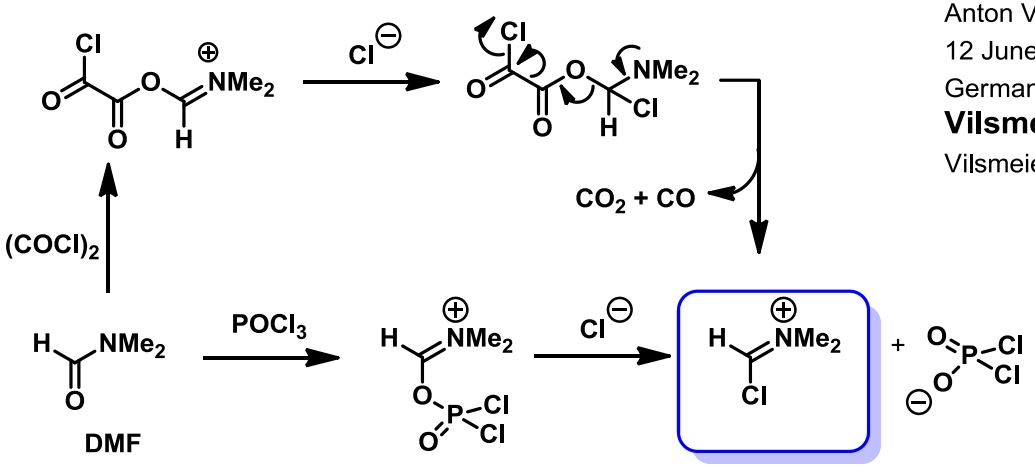
Acetilnitrato (anidride mista) usata per nitrare evitando amb. fortemente acido!

SO_3 -Piridina complesso anidfride solforica in piridina per solfonare evitando amb. acido

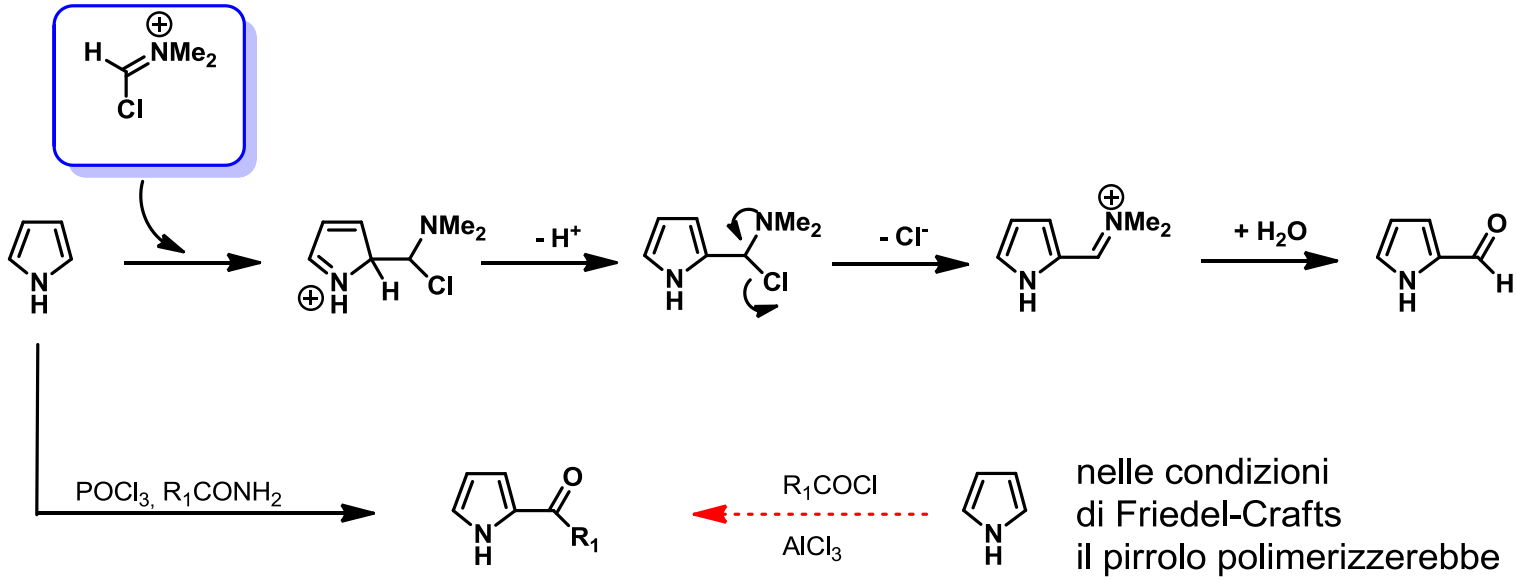
Ac_2O per acetilare senza Ac. di Lewis

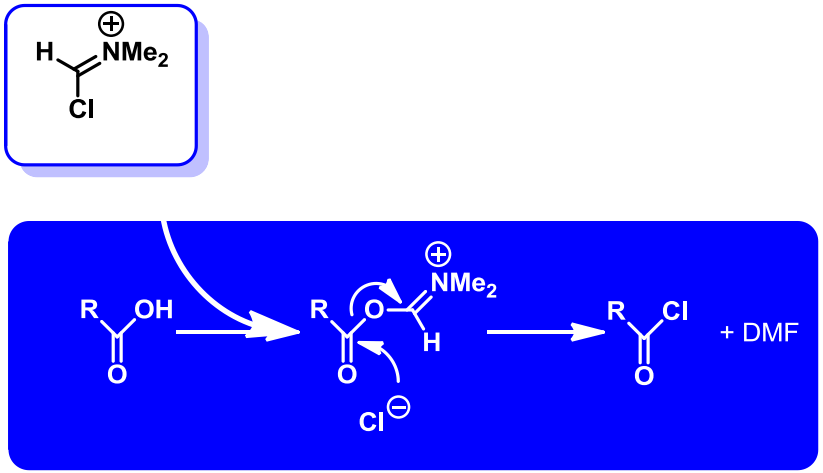
Vilsmeier-Haack 2-formil pirrolo

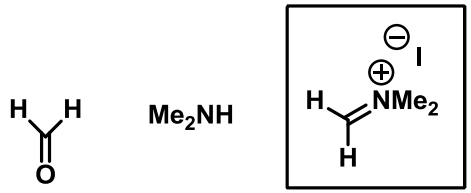
Eschenmoser base di Mannich



Anton Vilsmeier
12 June 1894 – 12 February 1962
German, b. Burgweinting bei Regensburg, Germany
Vilsmeier-Haack-Arnold reaction
Vilsmeier, A.; Haack, A., Chem. Ber. 1927, 60, 119


NMe2
Cl
- H+
- Cl-
+ H2O
POCl3, R1CONH2
R1COCl
AlCl3
nelle condizioni
di Friedel-Crafts
il pirrolo polimerizzerebbe

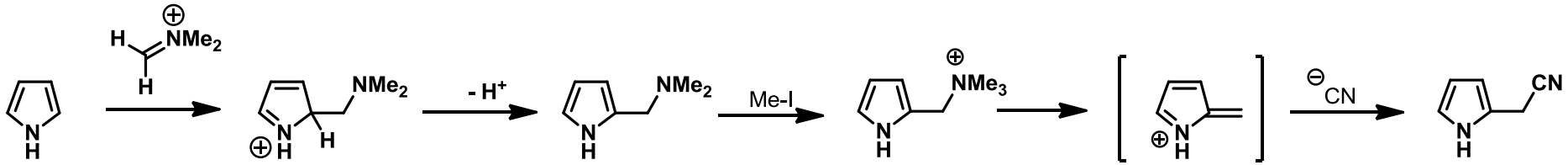

NMe2
Cl
R
OH
O
H
+ DMF



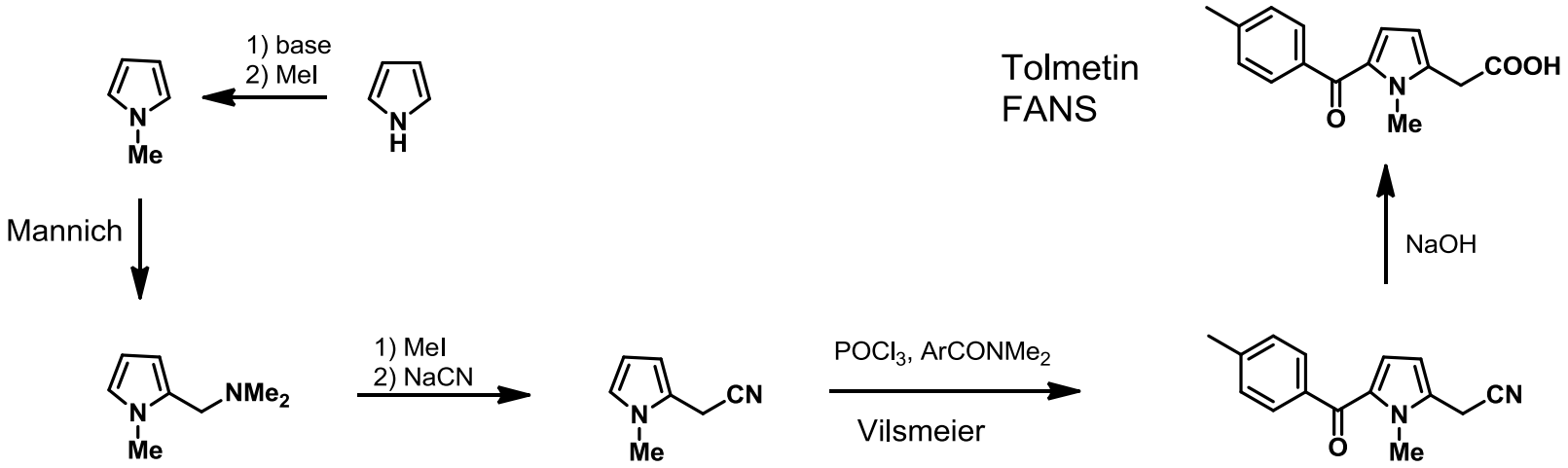
sale di **Eschenmoser**
commercializzato

≡ $E^{\oplus}$

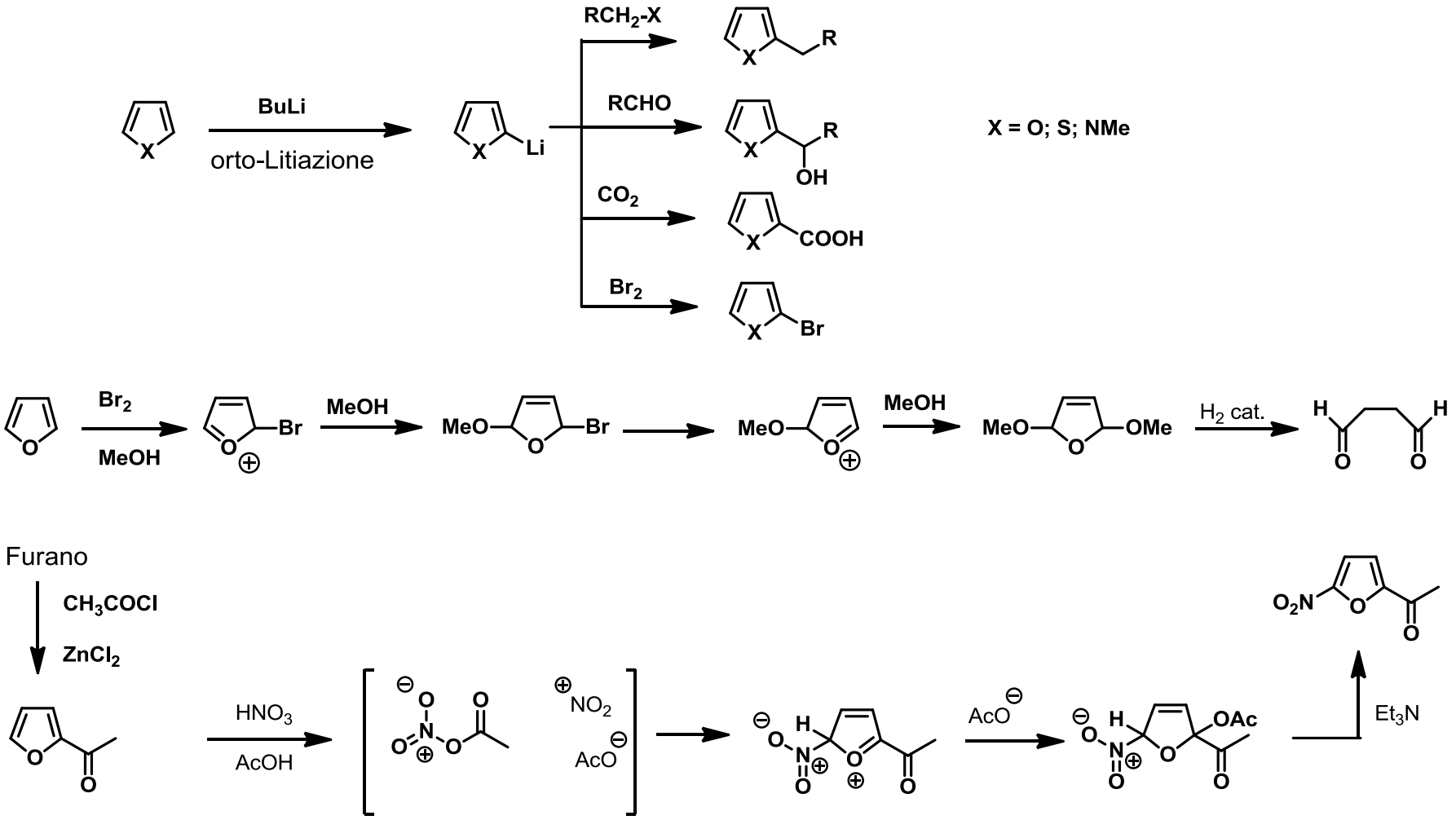
Carl Ulrich Franz Mannich
8 March 1877 - 5 March 1947
German, b. Breslau, Germany, now Wroclaw, Poland
Mannich reaction
Mannich, C.; Krosche, W., Arch. Pharm. 1912, 250, 647

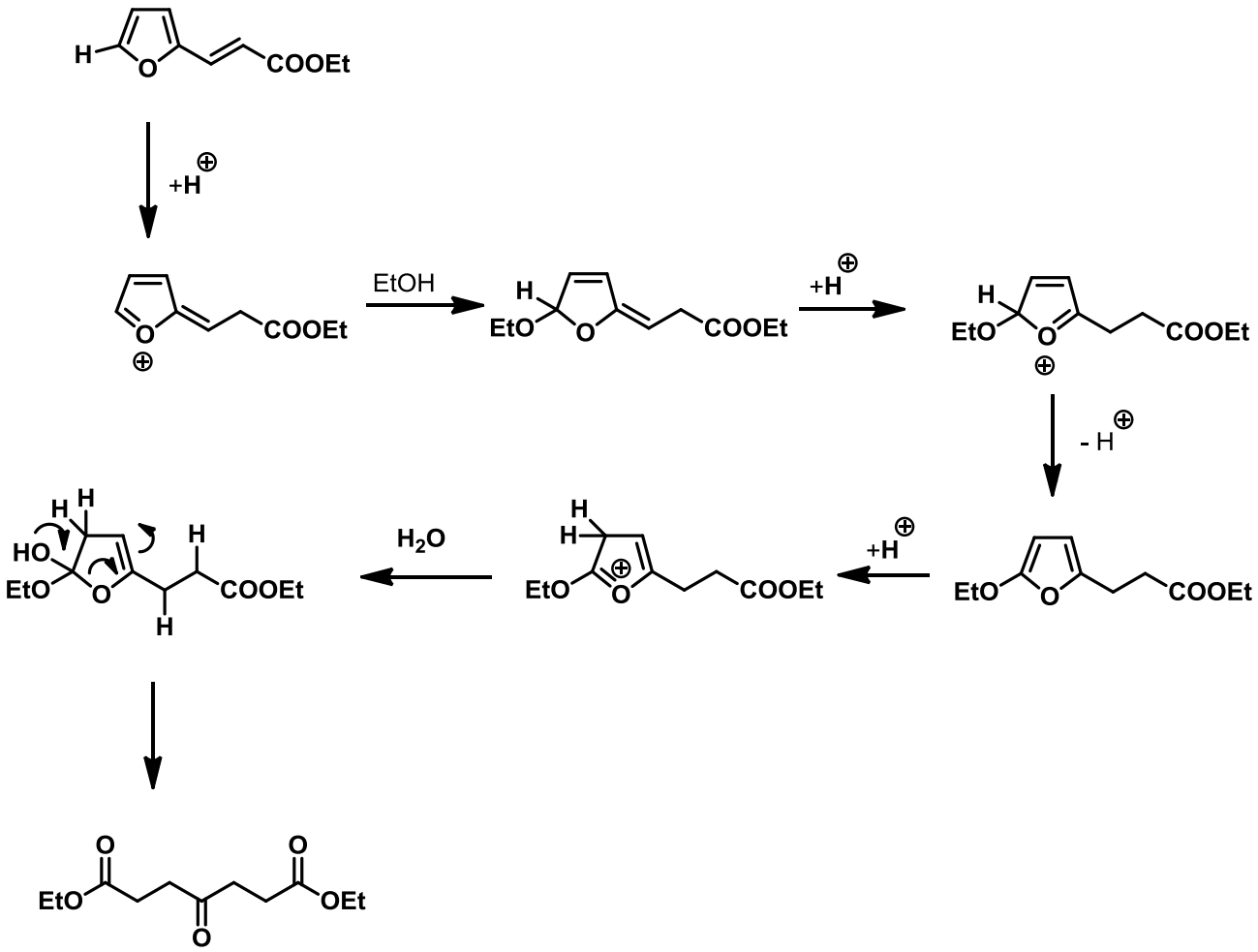


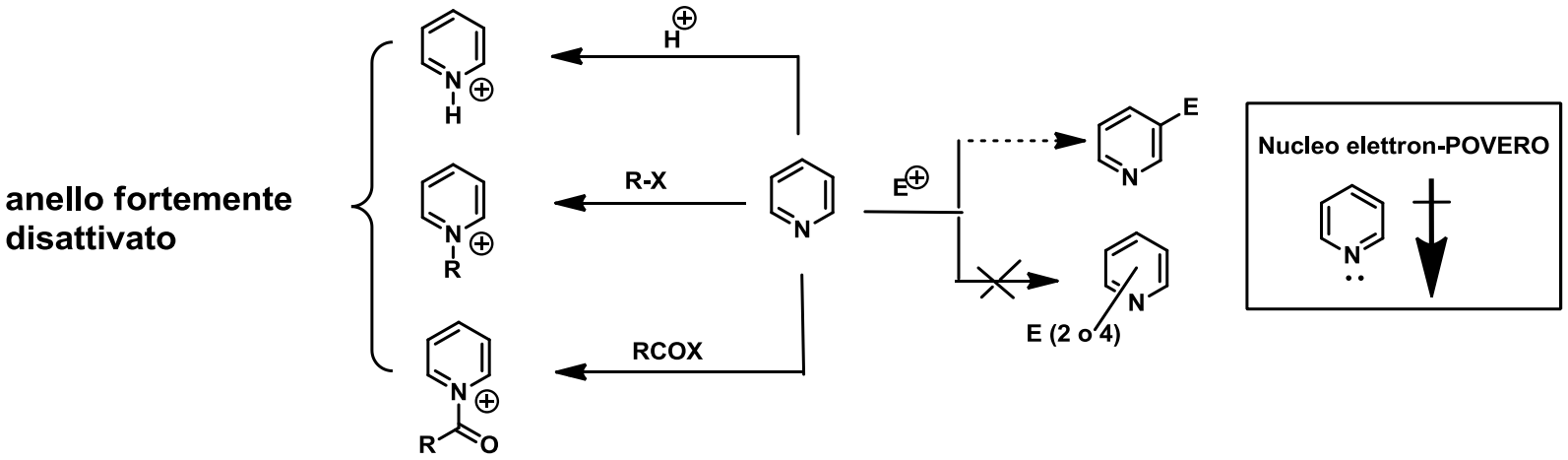
base di MANNICH

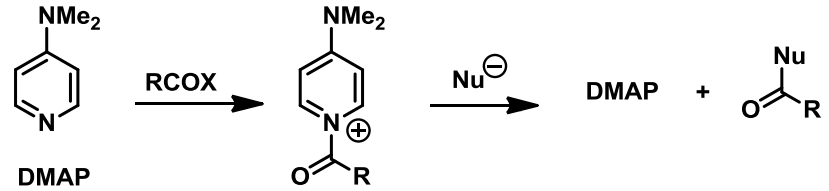


Il FURANO e N-Boc PIRROLO hanno scarso carattere aromatico: con anidride maleica partecipano come dieni nelle cicloaddizioni di Diels-ALDER (non il pirrolo e il tiofene!)

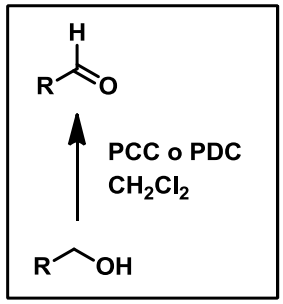


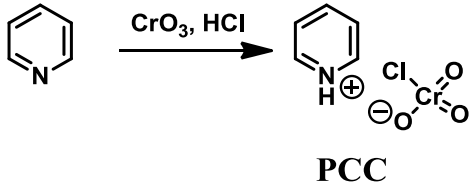

H
O
COOEt
+H
EtOH
EtO
- H
H_2O
HO
EtO
OEt





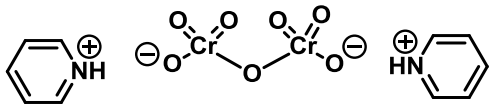
Meccanismo con cui la DMAP catalizza le sostituzioni nucleofile aciliche

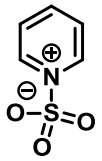




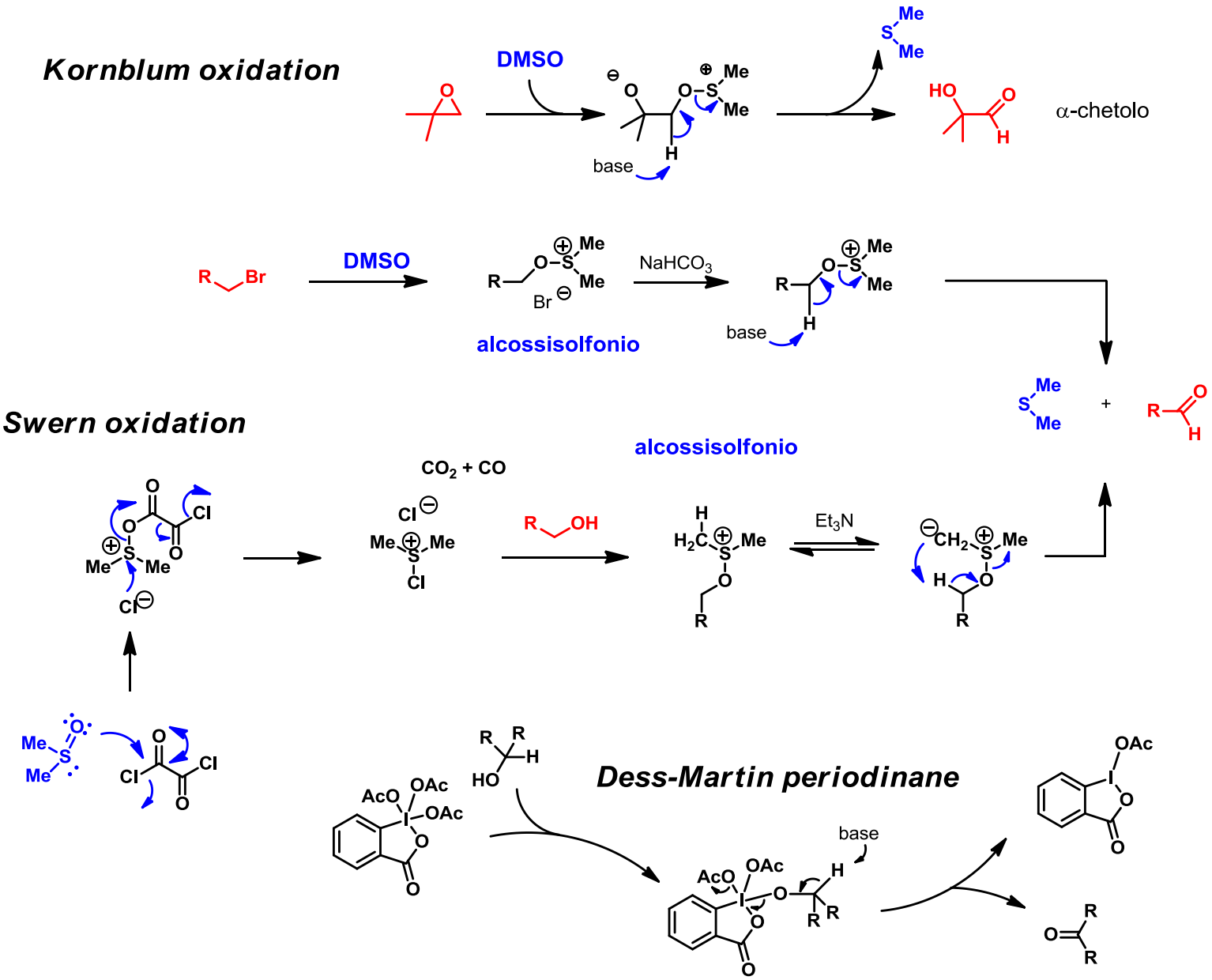
PCC

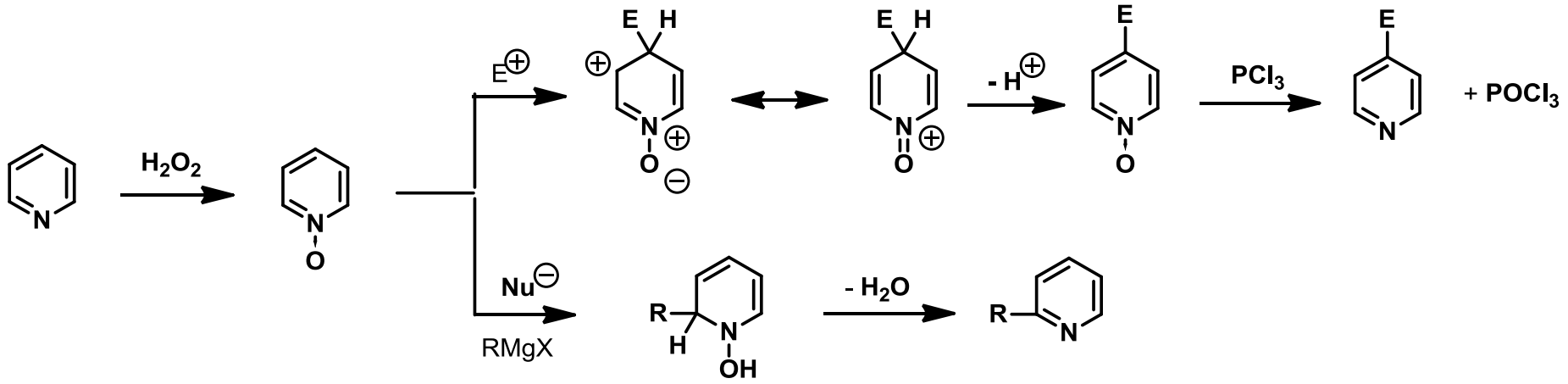
PDC

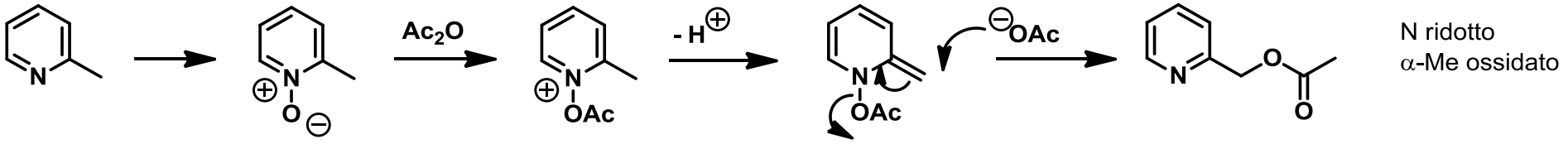


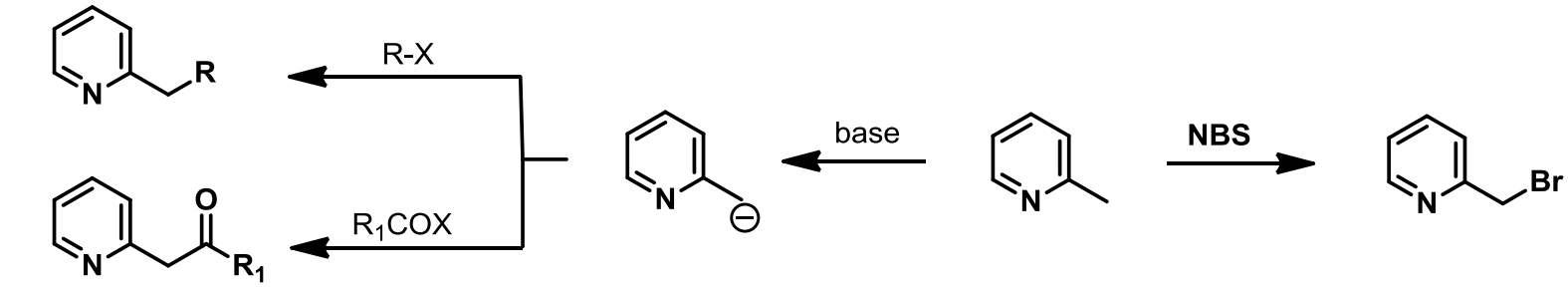


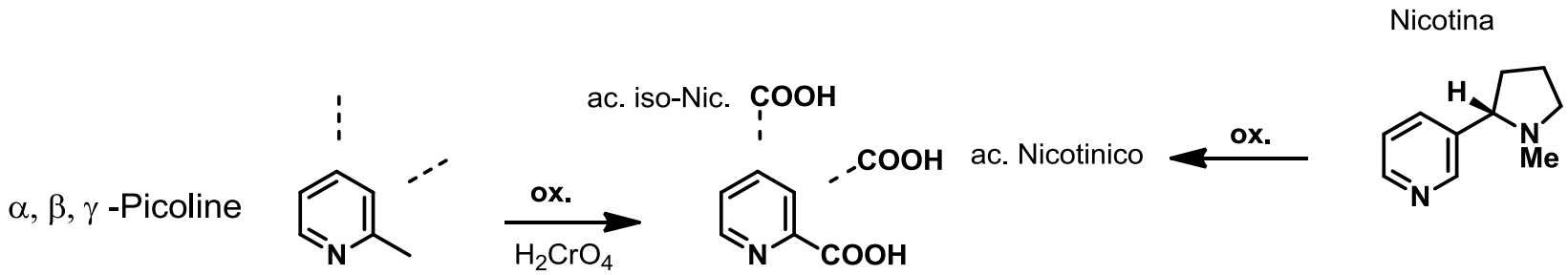
Py-SO_3 (per solfonare eterocicli)


Kornblum oxidation
DMSO
base
α-chetolo
DMSO
NaHCO3
base
alcossisolfonio
Swern oxidation
alcossisolfonio
CO2 + CO
Et3N
Dess-Martin periodinane
base


H2O2
E⊕
Nu⊖
RMgX
- H⊕
PCl3
+ POCl3
- H2O
E H
R
OH


Ac2O
- H⊕
⊖OAc
OAc
N ridotto
α-Me ossidato

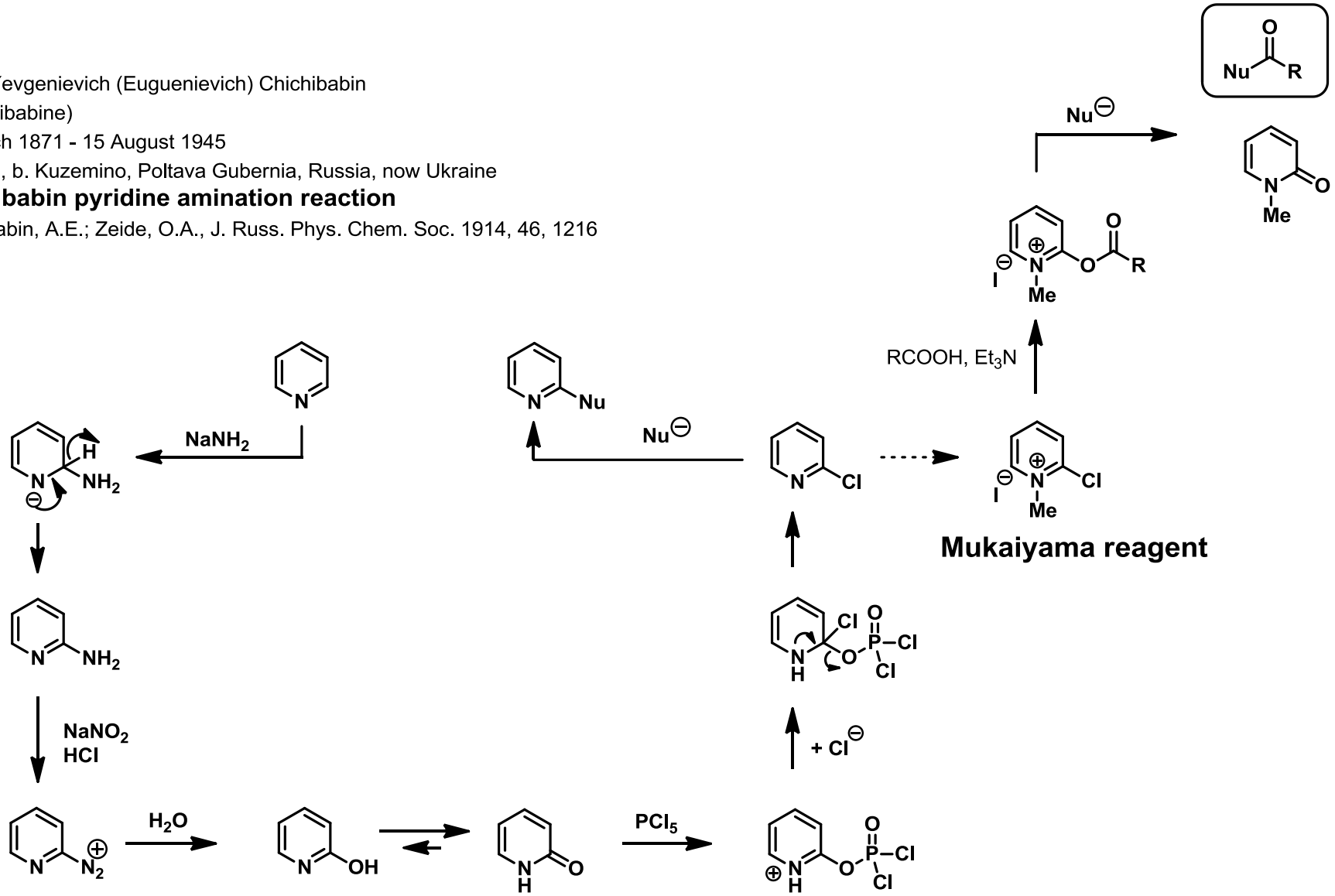

R-X
R
N
O
N
R1
R1COX
base
NBS
Br

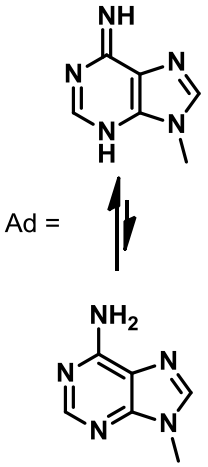

Nicotina
H
N
Me
ox.
ac. Nicotinico
ac. iso-Nic.
COOH
COOH
α, β, γ -Picoline
ox.
H2CrO4
N
COOH

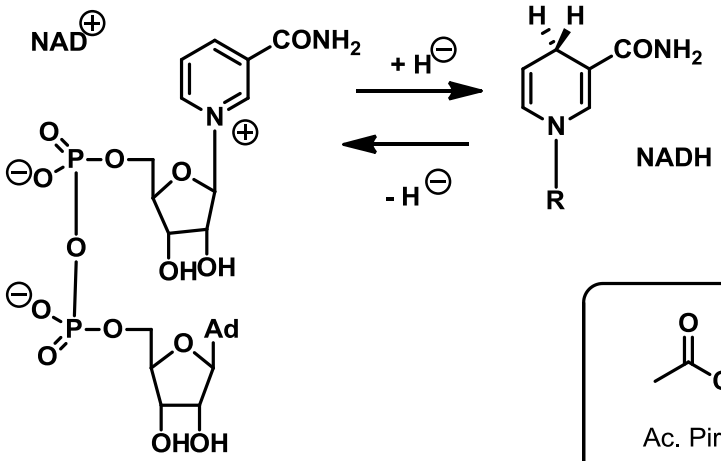
Alexei Yevgenievich (Euguenievich) Chichibabin
(Tchitchibabine)
17 March 1871 - 15 August 1945
Russian, b. Kuzemino, Poltava Gubernia, Russia, now Ukraine

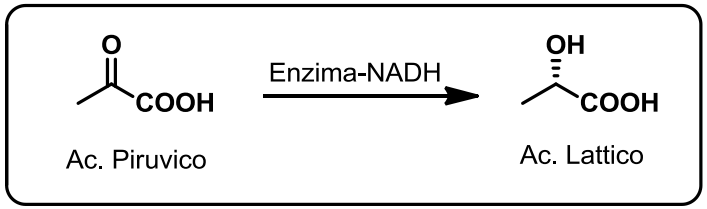
Chichibabin pyridine amination reaction

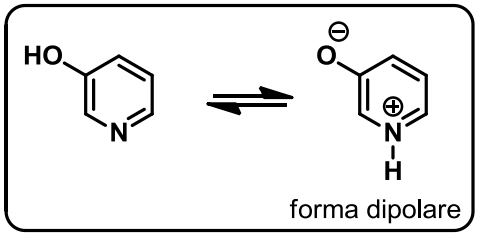
Chichibabin, A.E.; Zeide, O.A., J. Russ. Phys. Chem. Soc. 1914, 46, 1216

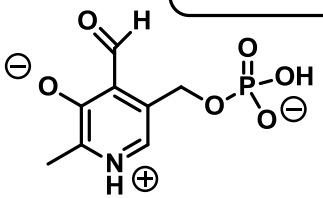




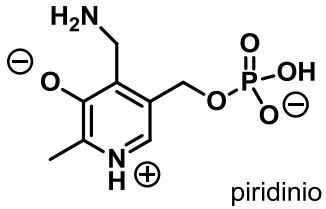






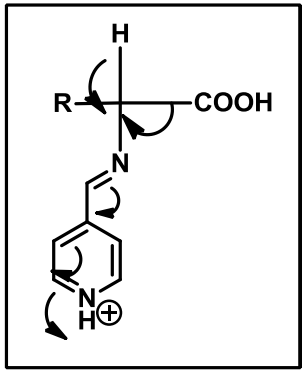


PIRIDOSSALE_FOSFATO (PLP)

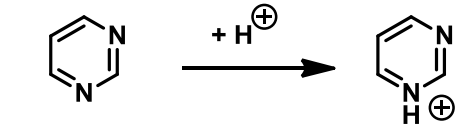


piridinio zwitter a pH fis.

PIRIDOSSAMMINA

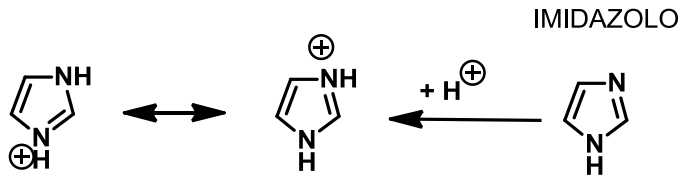


Cofattori in
decarbossilasi e
amminotransferasi

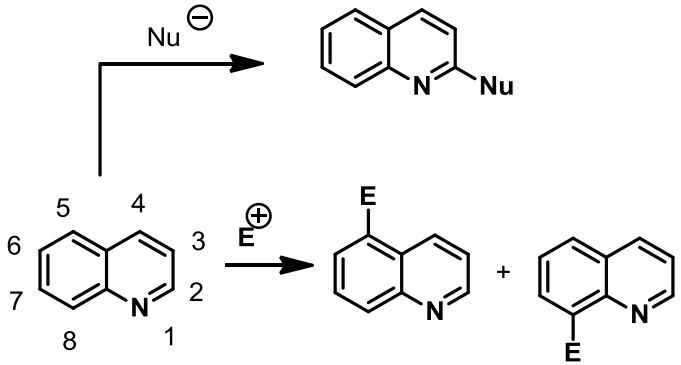


PIRIMIDINA

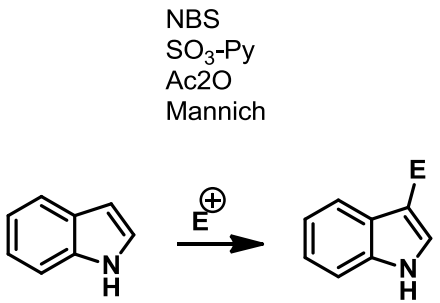
PIRIMIDINIO pKa 1,5

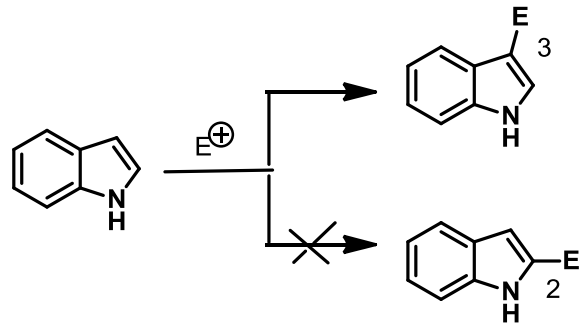


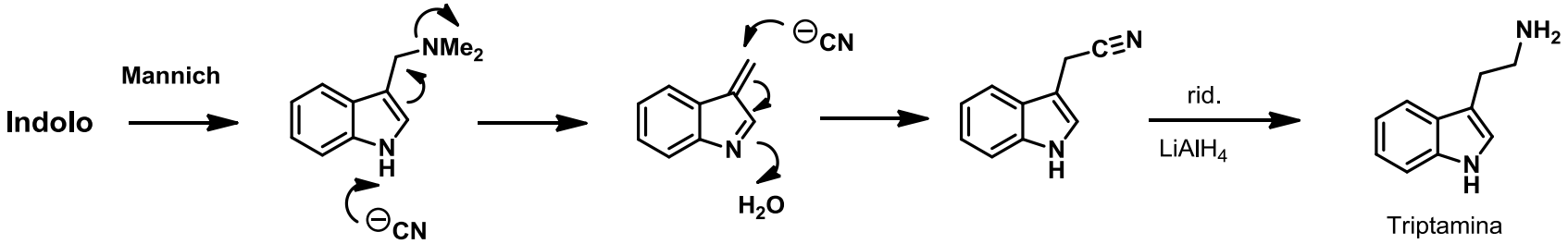
IMIDAZOLIO pKa 6,9



CHINOLINA





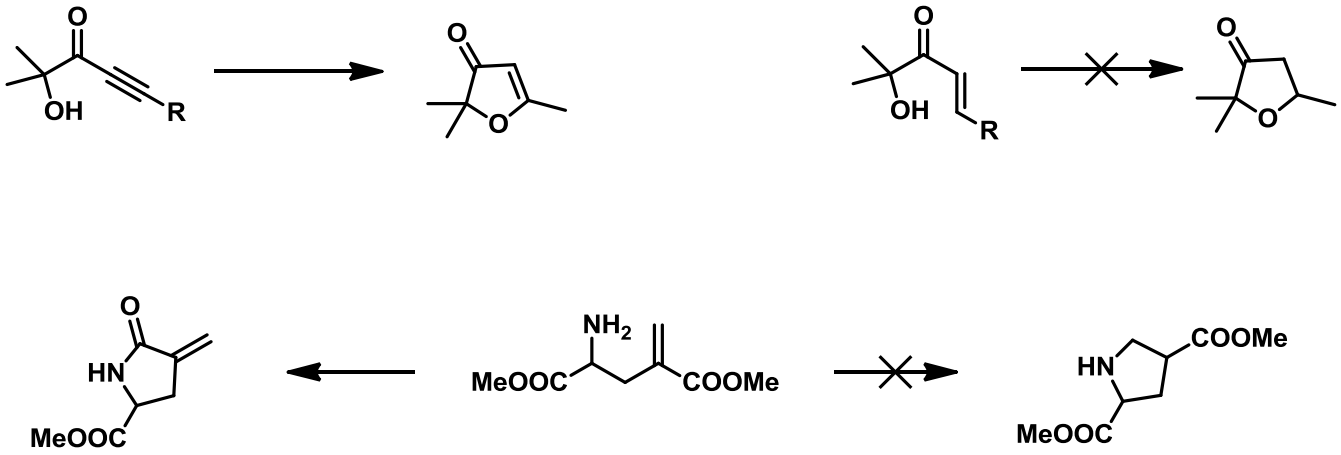


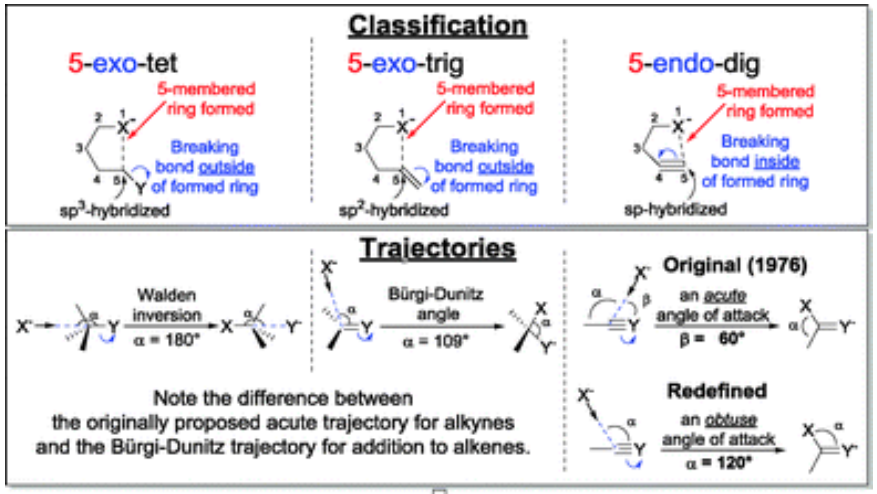
Nella preparazione di eterocicli aromatici sono coinvolte specie nucleofile all'*N, O, S* che intercettano gruppi elettrofilici.

Reazioni intramolecolari *(entropicamente favorite)* portano alla formazione di anelli a 5 o 6 termini#

I prodotti di ciclizzazione sono (o diventano facilmente) aromatici

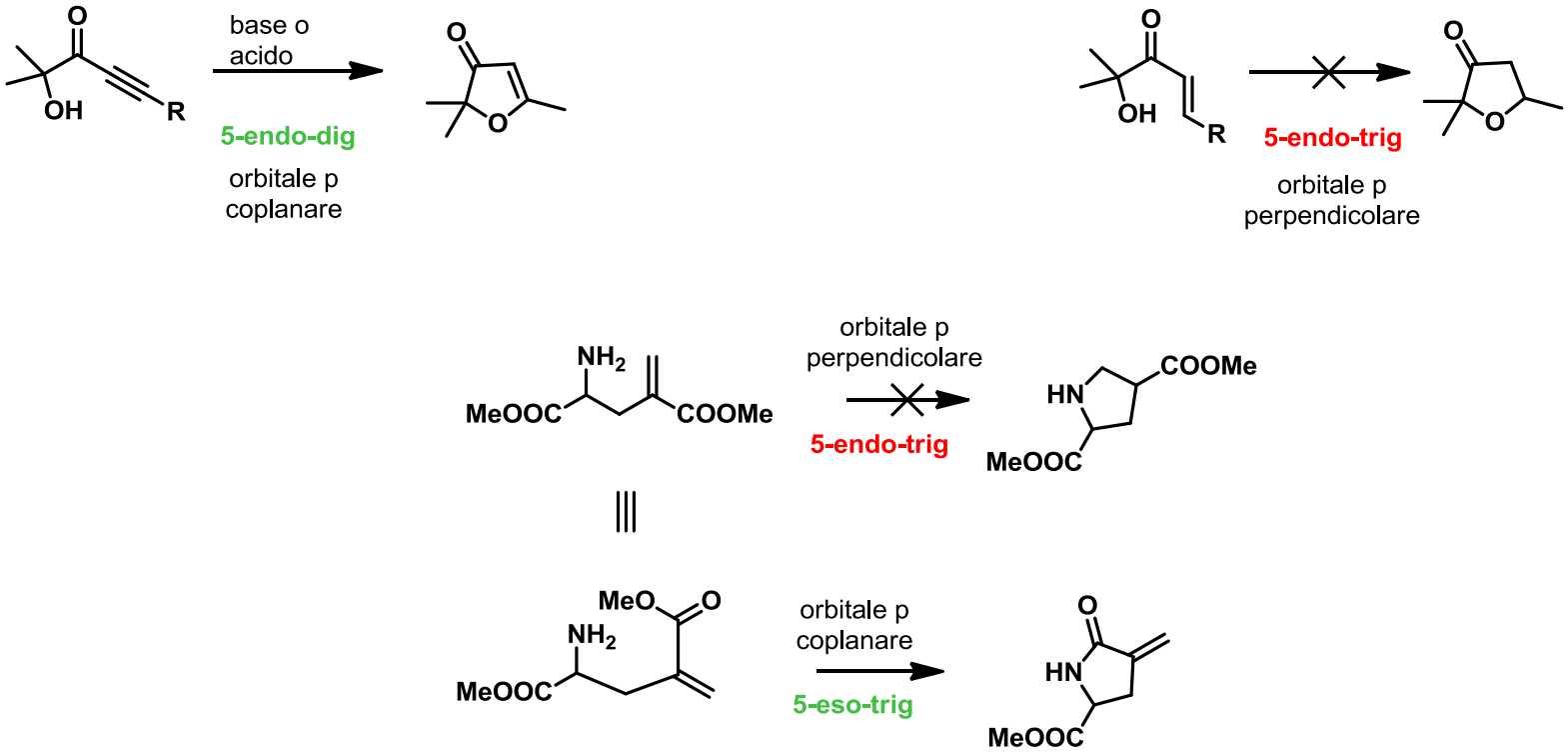
#*Regole per la formazione di anelli formulate nel 1976 da Sir Jack Baldwin*





		3	4	5	6
Tet	endo-	*a*	*a*	×	×
	exo-	✓	✓	✓	✓
Trig	endo-	×	×	×	✓
	exo-	✓	✓	✓	✓
Dig	endo-	✓	✓	✓	✓
	exo-	×	×	✓	✓

Baldwin's nomenclature for cyclization reactions (top) combined with the suggested trajectories for intramolecular nucleophilic attack (middle) yielded the list of favourable and unfavourable modes of cyclization (rules for ring closure, bottom). (a) = no prediction.



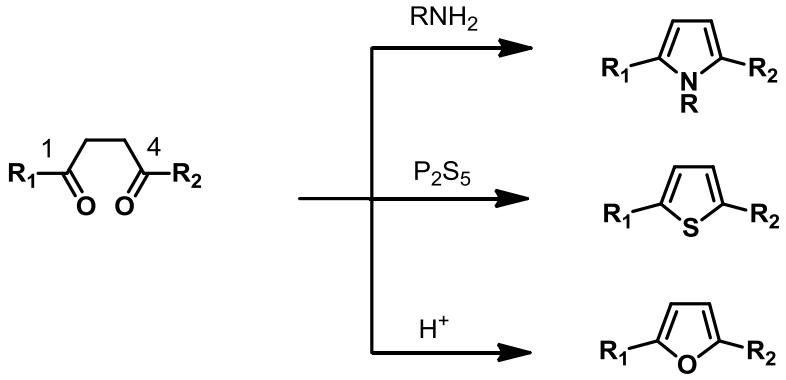
la formazione di anelli a 5

è **permessa** quando l'orbitale p (elettrofilico) giace sul piano del costruendo anello;

è **proibita** quando l'orbitale p (elettrofilico) risulta perpendicolare al piano del costruendo anello

Het.$_{Ar}$ con 1 eteroatomo

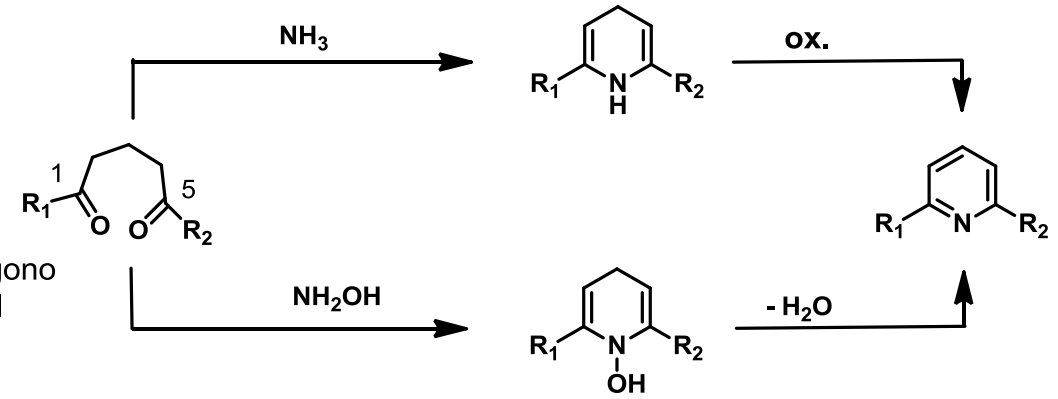
1,4-dicarbonili si ottengono
via addizioni di Michael
di "umpolung"



Paal-Knorr pyrrole synthesis

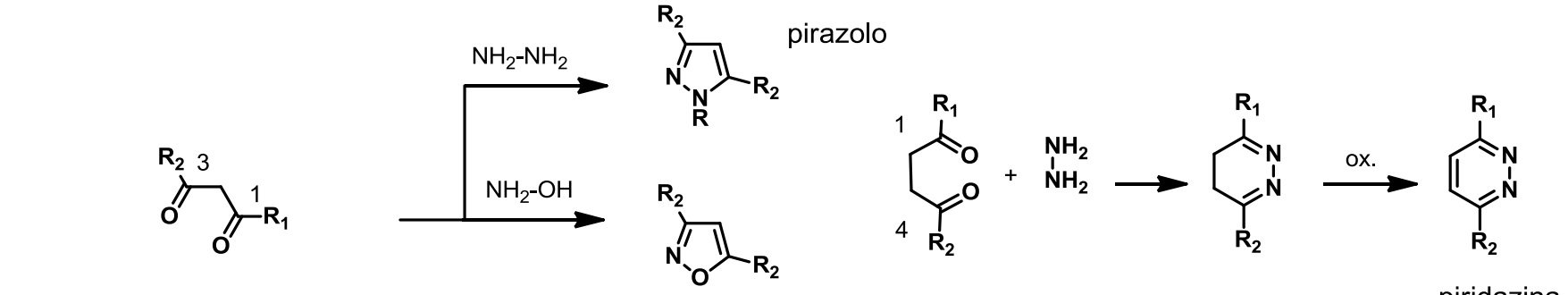
pentaatomici

1,5-dicarbonili si ottengono
via addizioni di Michael



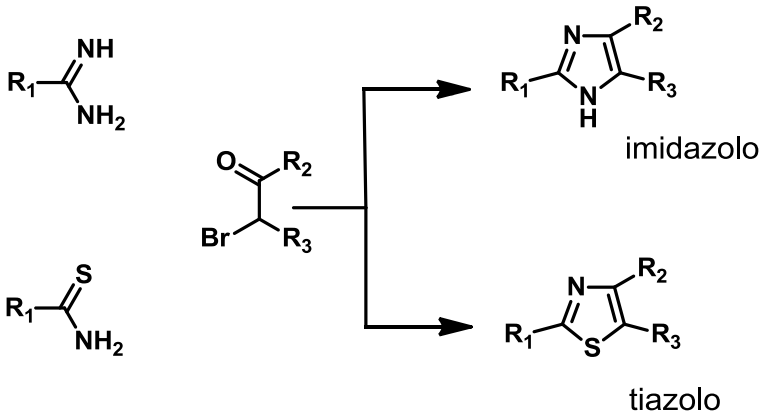
esaatomici

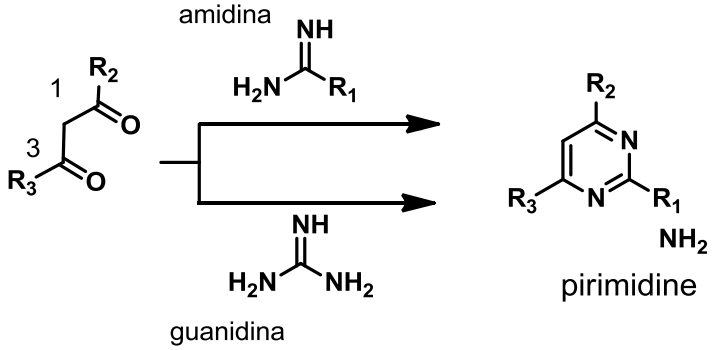
H_{Ar} con 2 eteroatomi adiacenti



1,3-dicarbonili prodotti
via condensazione di Claisen

H_{Ar} con 2 eteroatomi NON adiacenti

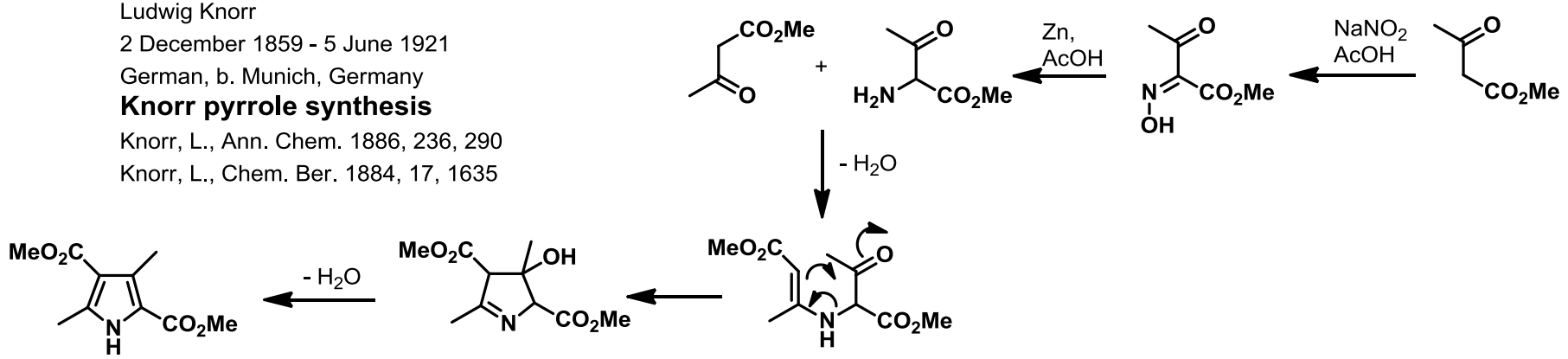




Ludwig Knorr
2 December 1859 - 5 June 1921
German, b. Munich, Germany

Knorr pyrrole synthesis

Knorr, L., Ann. Chem. 1886, 236, 290
Knorr, L., Chem. Ber. 1884, 17, 1635



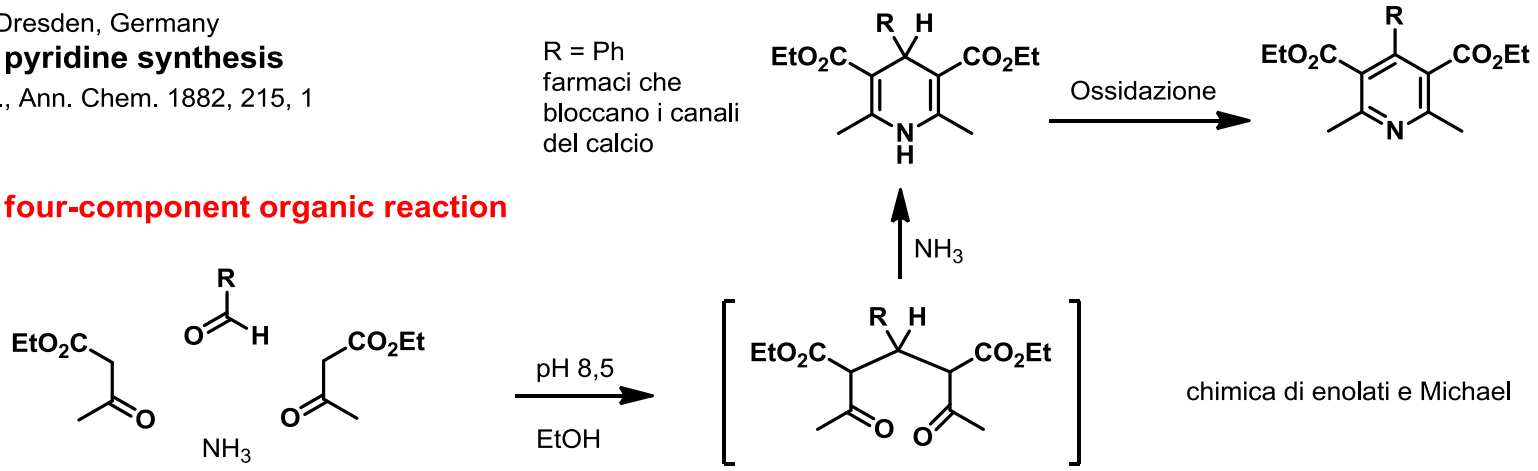
Arthur Rudolf Hantzsch
7 March 1857 - 14 March 1935
German, b. Dresden, Germany

Hantzsch pyridine synthesis

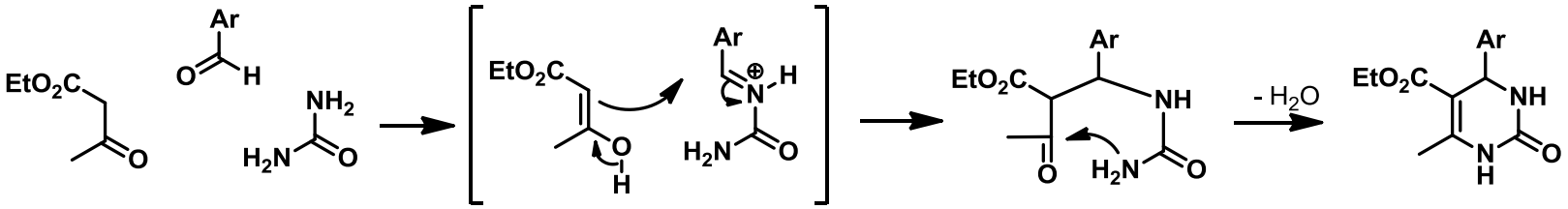
Hantzsch, A., Ann. Chem. 1882, 215, 1

R = Ph
farmaci che
bloccano i canali
del calcio

a four-component organic reaction



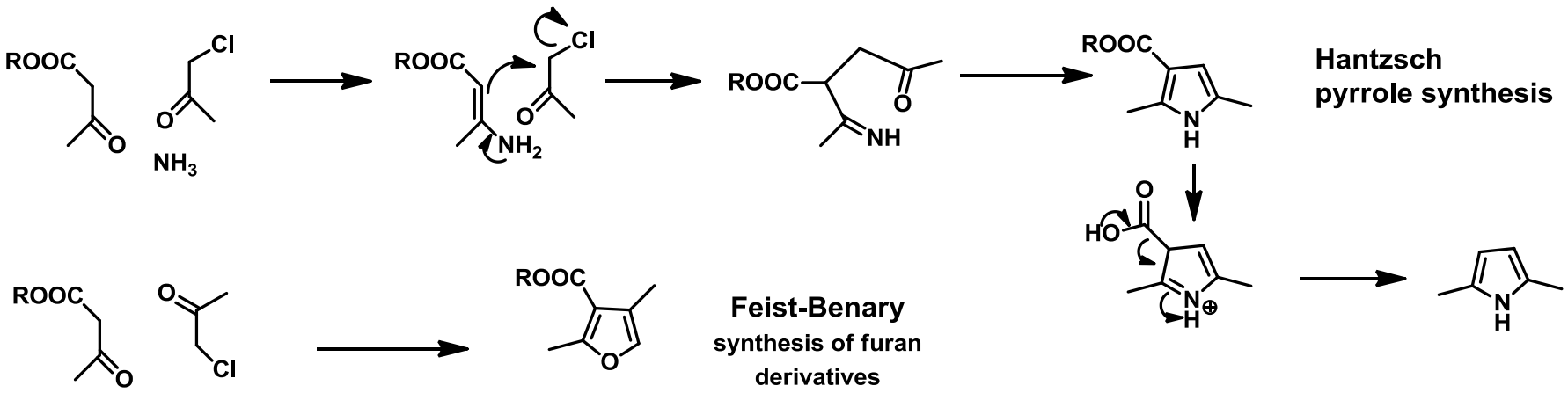
chimica di enolati e Michael

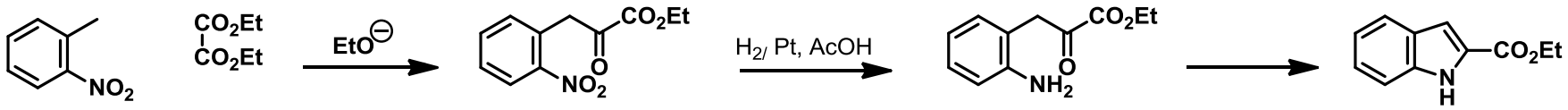


Biginelli reaction

3,4-diidropirimidin-2(1H)-one

one-pot three-component organic reactions





Reissert Indole synthesis

A. Reissert, Ber. 30, 1030 (1897)

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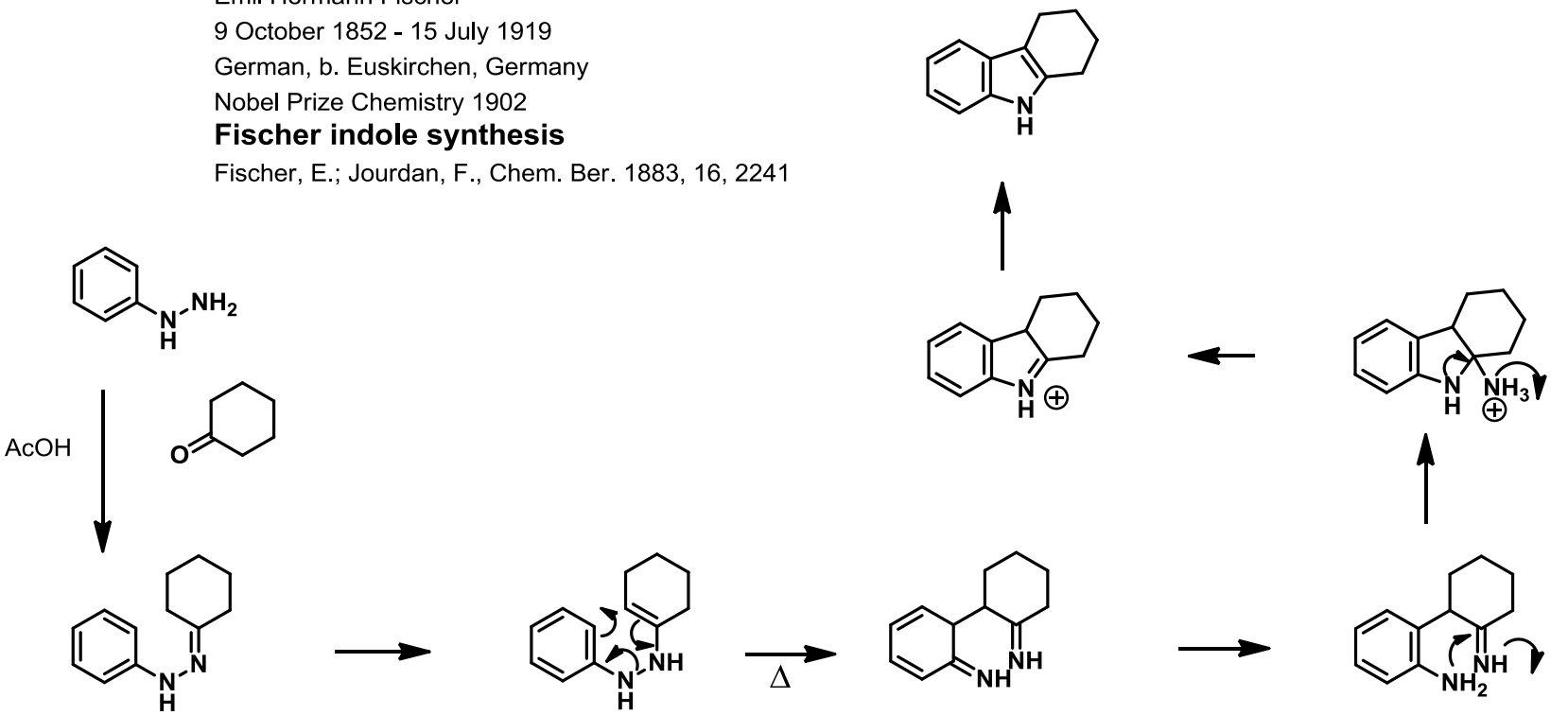
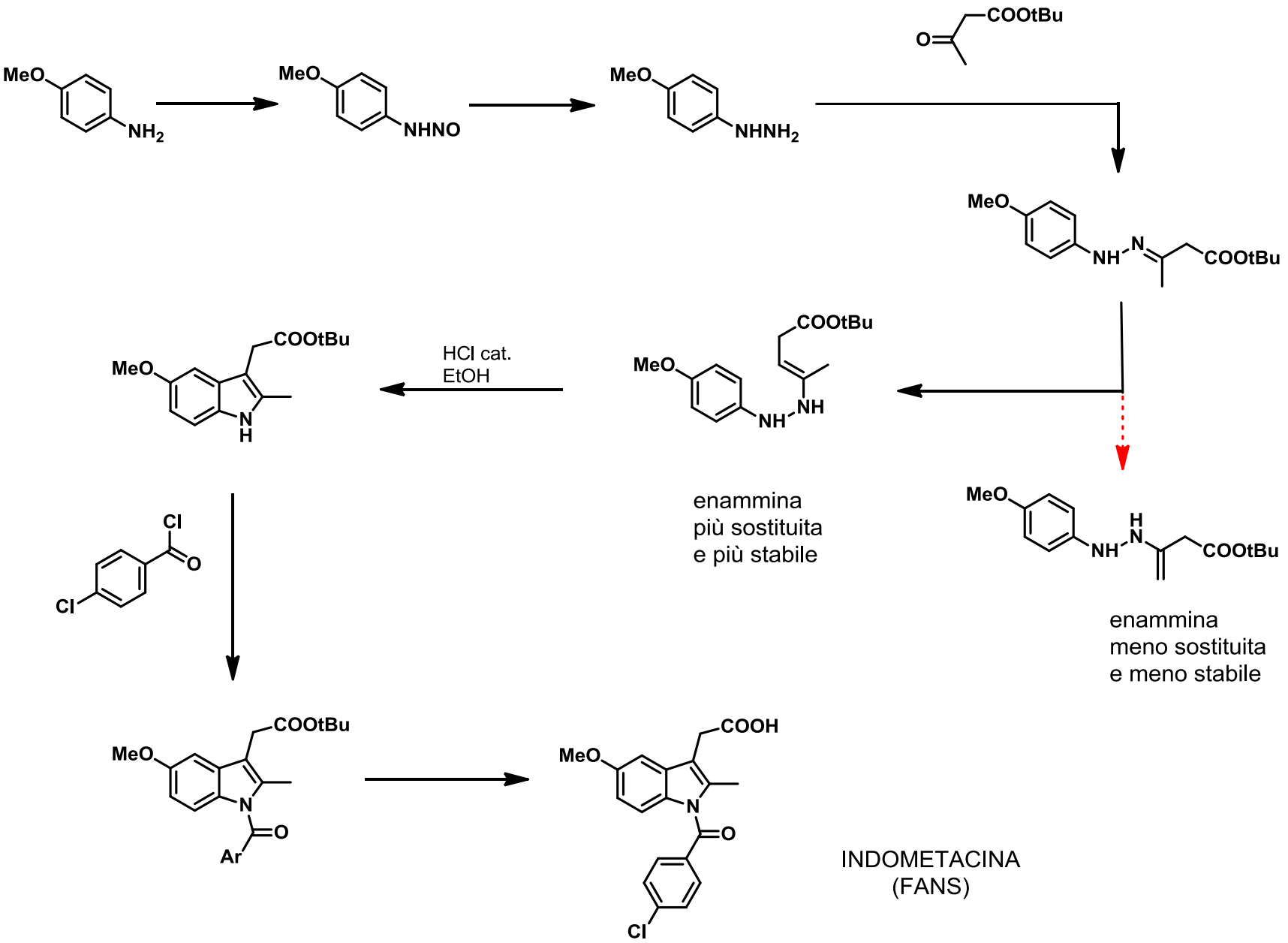
Emil Hermann Fischer
9 October 1852 - 15 July 1919
German, b. Euskirchen, Germany
Nobel Prize Chemistry 1902

Fischer indole synthesis

Fischer, E.; Jourdan, F., Chem. Ber. 1883, 16, 2241



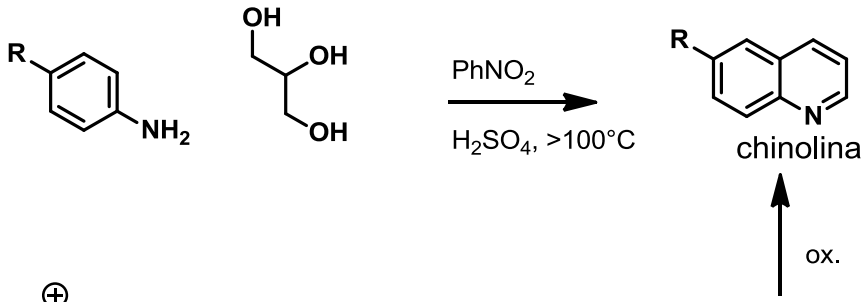
[3,3]-sigmatropico

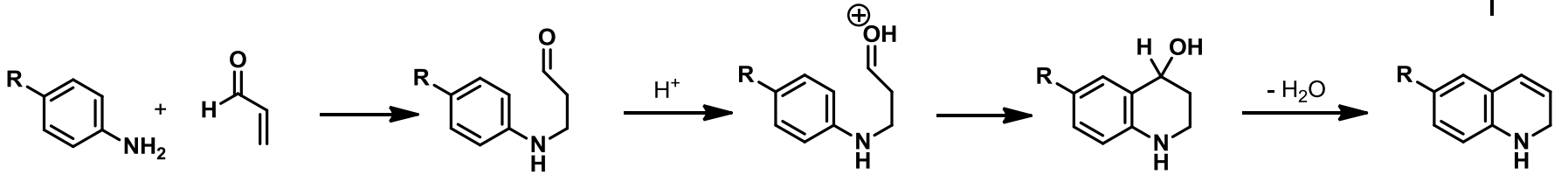

MeO
NH2
NHNO
NHNH2
COOtBu
O
NH
N
HCl cat.
EtOH
enammina
più sostituita
e più stabile
enammina
meno sostituita
e meno stabile
Cl
Ar
COOH
INDOMETACINA
(FANS)

Zdenko Hans Skraup
3 March 1850 - 10 September 1910
Czech, b. Prague, Czech Republic

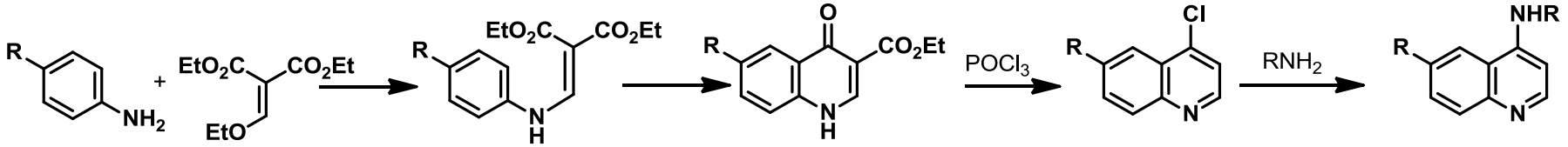
Skraup reaction

Skraup, Z.H., Chem. Ber. 1880, 13, 2086

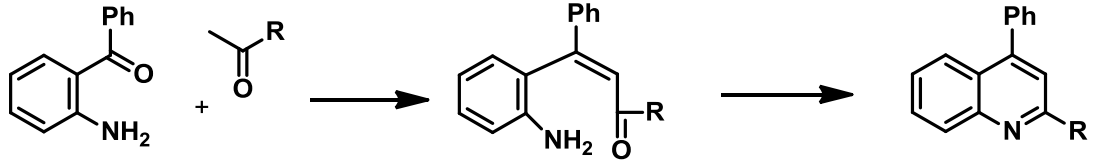




4-chinolone antibiotici



Friedländer



August Bischler
29 April 1865 – 26 May 1957
German-Swiss, b. Karlsruhe, Germany

Bernard Napieralski

Bischler-Napieralski synthesis

Bischler, A.; Napieralski, B., Chem. Ber. 1893, 26, 1903