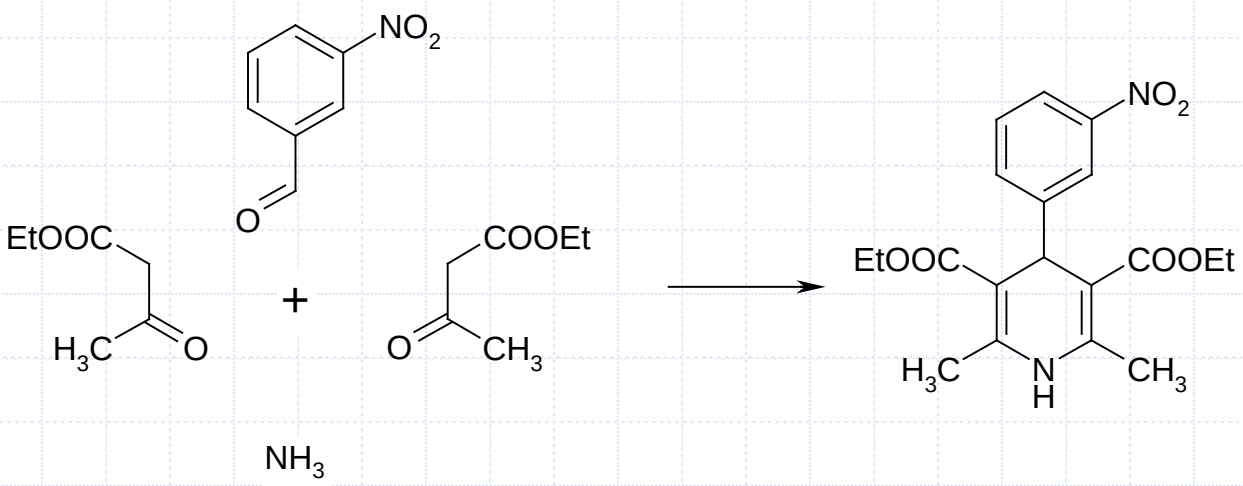
Univerza v Ljubljani
Fakulteta za farmacijo

Katedra za farmacevtsko kemijo

Ca-antagonist

Pregled sinteznega postopka



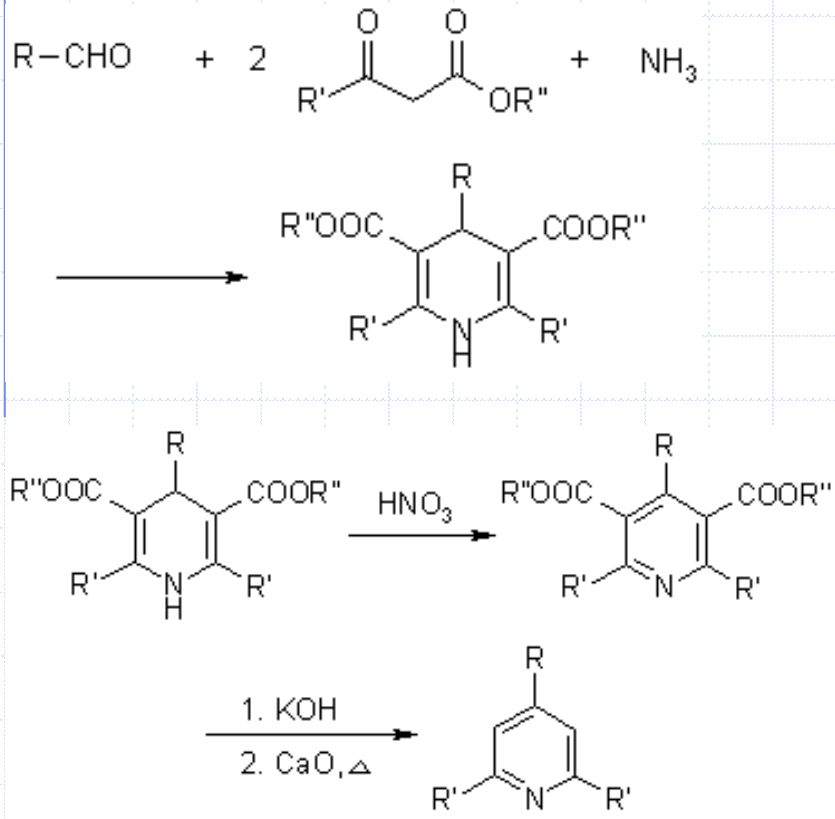
Multikomponentna reakcija:

Aldehid + amin + 2 ekv β-keto-ester

Hantzsch, 1881

Mehanizem Hantzscheve sinteze

Hantzsch Dihydropyridine (Pyridine) Synthesis

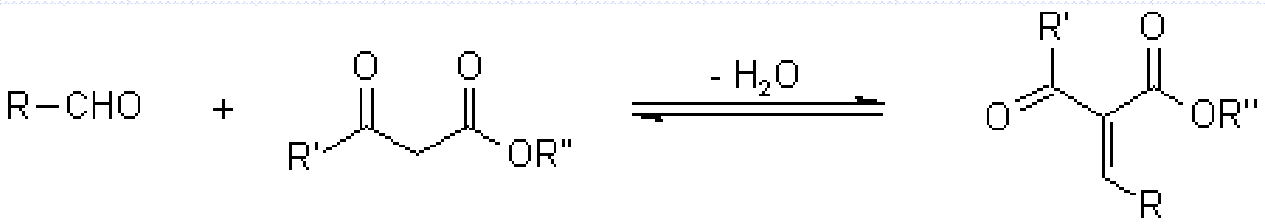


This reaction allows the preparation of dihydropyridine derivatives by condensation of an aldehyde with two equivalents of a β-ketoester in the presence of ammonia. Subsequent oxidation (or dehydrogenation) gives pyridine-3,5-dicarboxylates, which may also be decarboxylated to yield the corresponding pyridines.

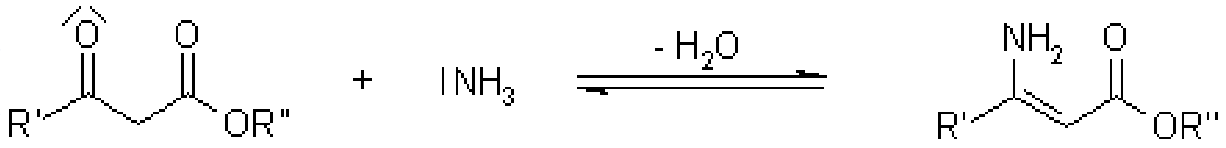
http://www.organic-chemistry.org/namedreactions/hantzsch-dihydropyridine-synthesis.shtm

Mehanizem Hantzscheve sinteze

1. Aldehid + 1 ekv β-keto estra: Knoevenaglova kondenzacija

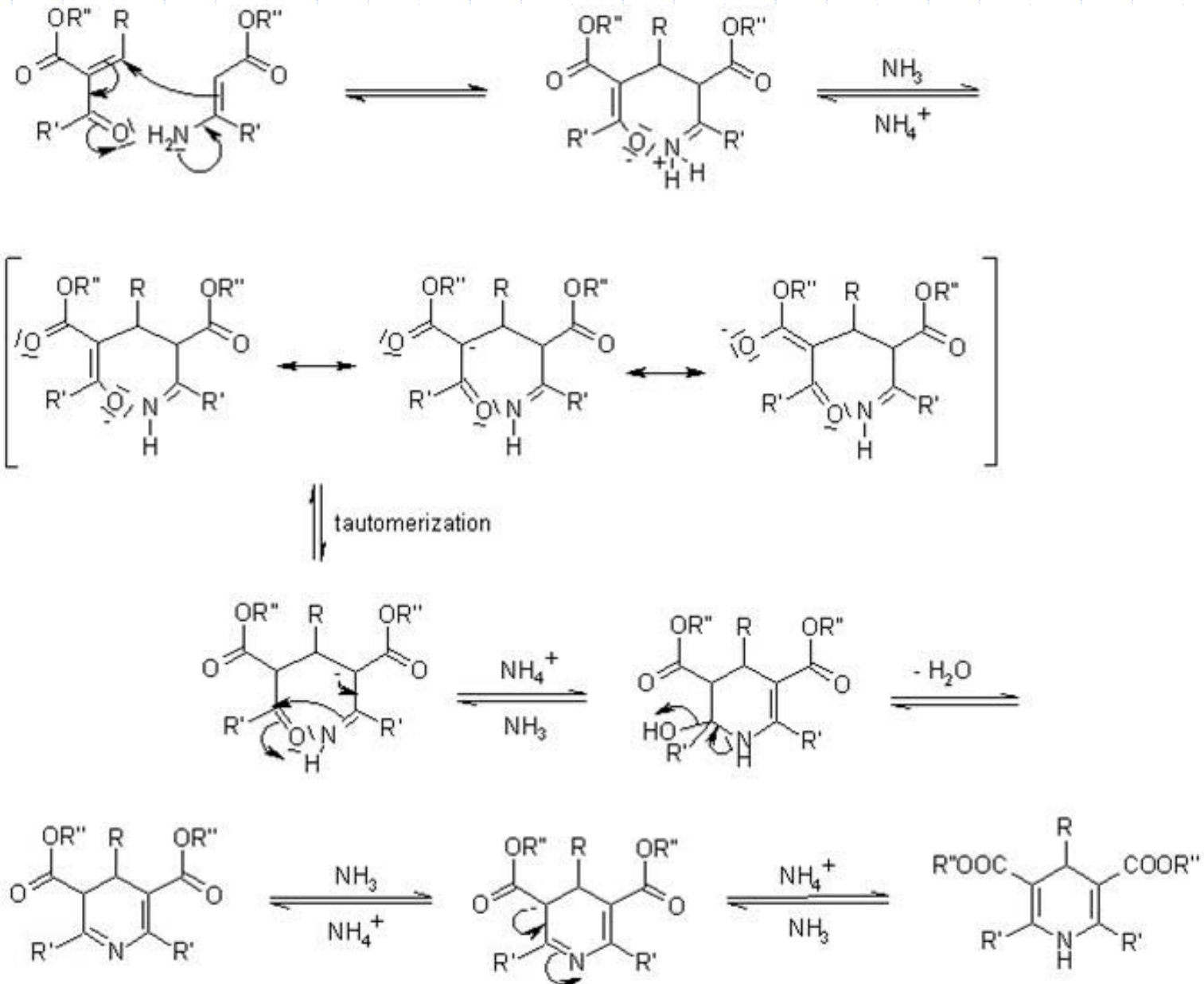


2. Amin + 1 ekv β-keto estra: adicija s sledečo eliminacijo: tvorba imina (tavt. enamin)



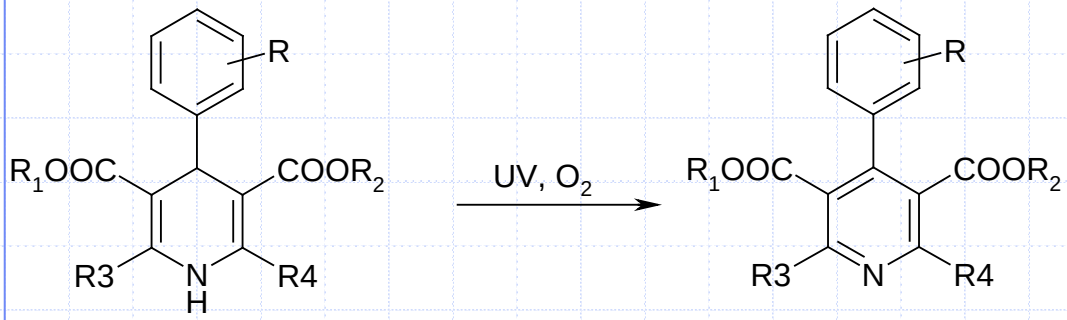
http://www.organic-chemistry.org/namedreactions/hantzsch-dihydropyridine-synthesis.shtm

3. Michaelova adicija (1,4-adicija) enamina na α,β-nenasičen keton (prebiten NH_3 kot katalizator)



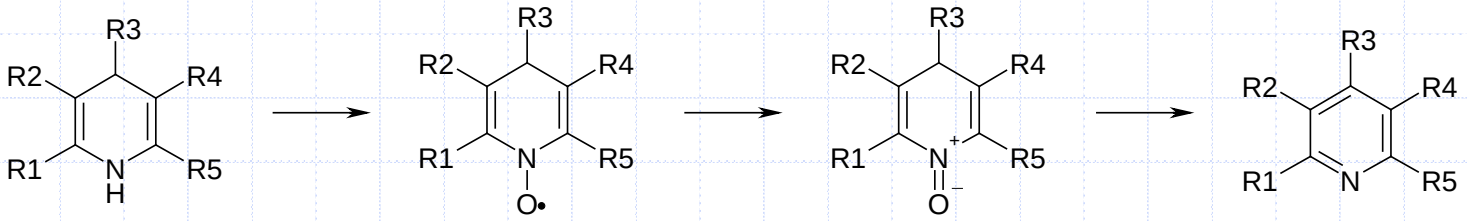
Lastnosti 1,4-dihidropiridinov

Občutljivi na oksidante: oksidacija do piridinov



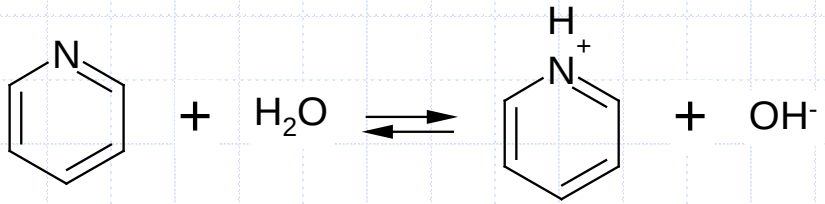
Učinkovine zaščitene pred svetlobo!

Mehanizem: preko nitroksidnega radikala



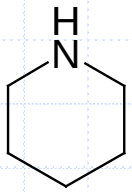
Lastnosti piridinov

Šibka baza:



$pK_a = 5,2$

$(pK_b = 8,8)$

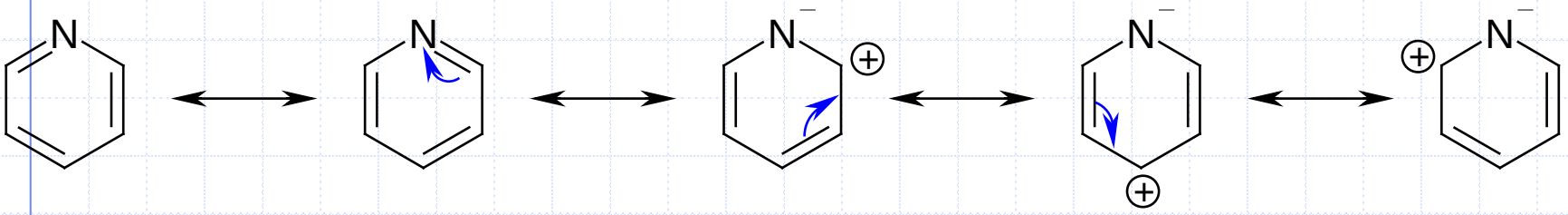


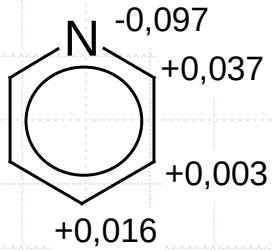
piperidin: $pK_a = 11,1$

$(pK_b = 3,9)$

Reaktivnost piridinov

Manjša elektronska gostota obročnih C zaradi prisotnosti bolj elektronprivlačnega N atoma





⇒ manjša reaktivnost za elektrofilne aromatske substitucije

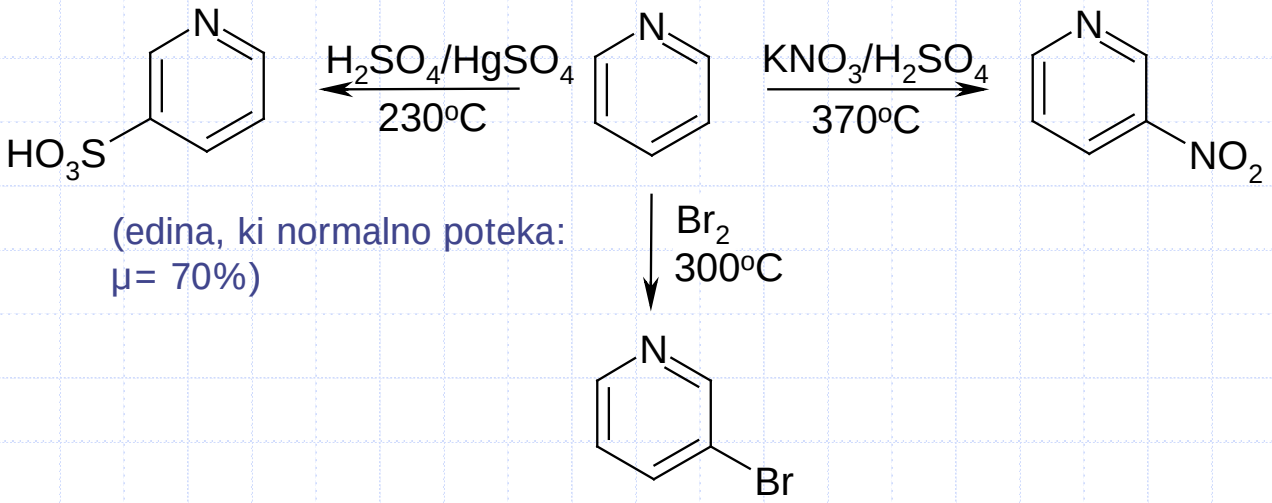
⇒ SE_{Ar} potekajo na m-mesto

⇒ bolj občutljiv za nukleofile

⇒ SN_{Ar} potekajo na o- in p- mesto

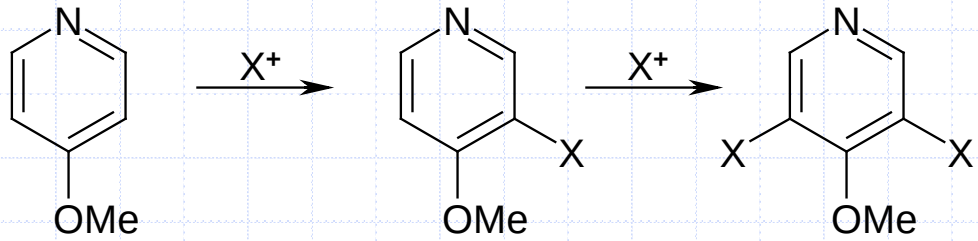
Reaktivnost piridinov

SE_{Ar}: zgolj pod zelo ostrimi reakcijskimi pogoji

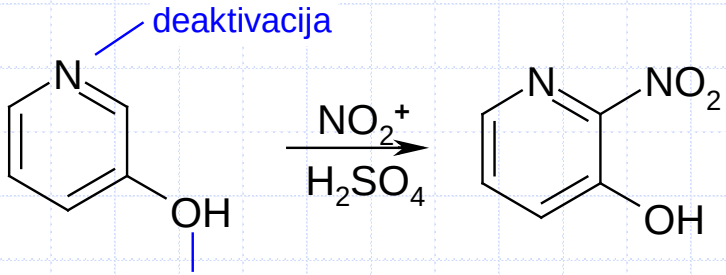


(edina, ki normalno poteka: μ= 70%)

Skupine, ki aktivirajo za SE_{Ar}:

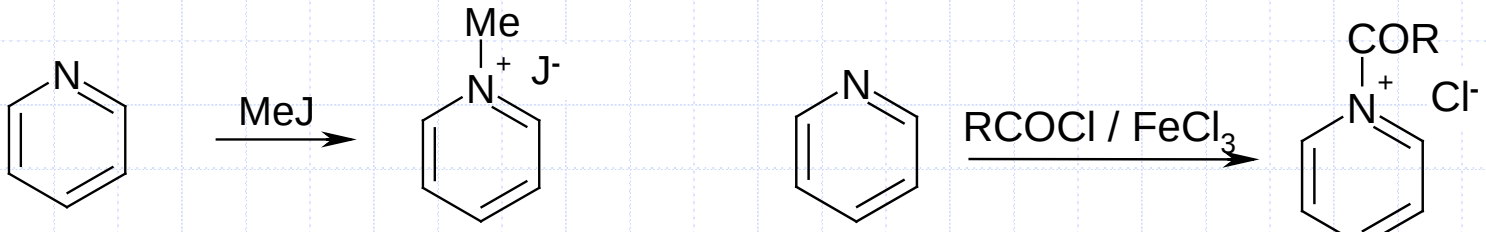


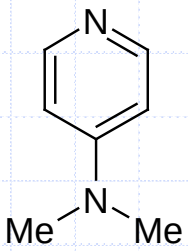
X = Cl, Br, NO_2, SO_3H



Reaktivnost piridinov

Friedel-Crafts-ove reakcije ne potekajo!
Alkiliranje in aciliranje poteče na obročni N-atom
→ piridinijeve soli

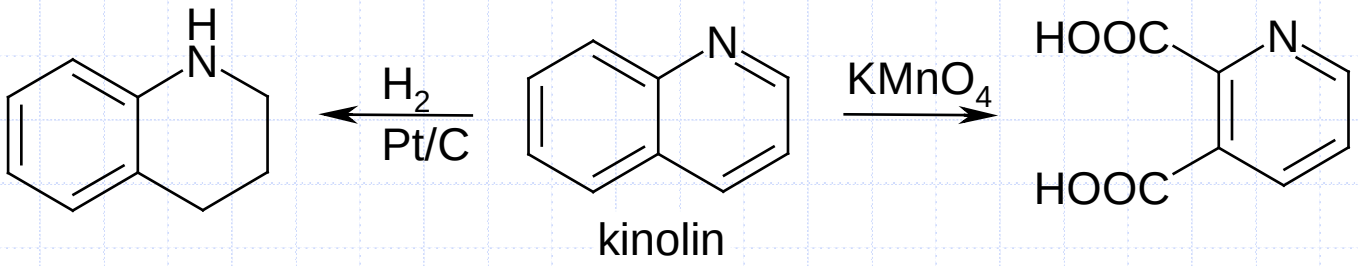




DMAP

Reaktivnost piridinov

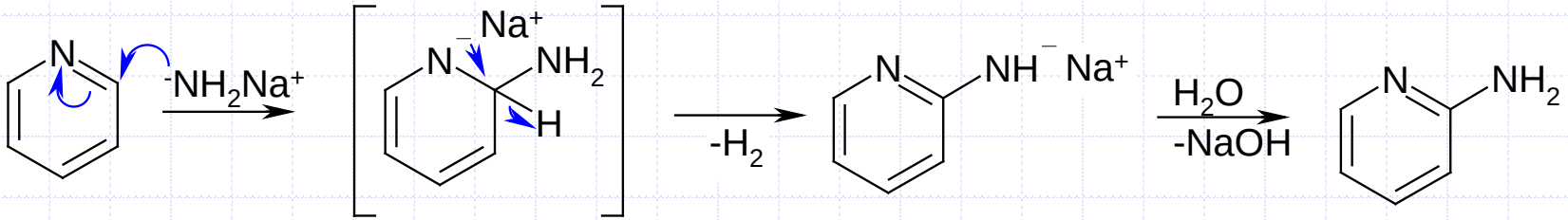
Piridin je bolj obstojen napram oksidacijam kot benzen, lažje pa ga reduciramo (velja za vse heteroaromate):



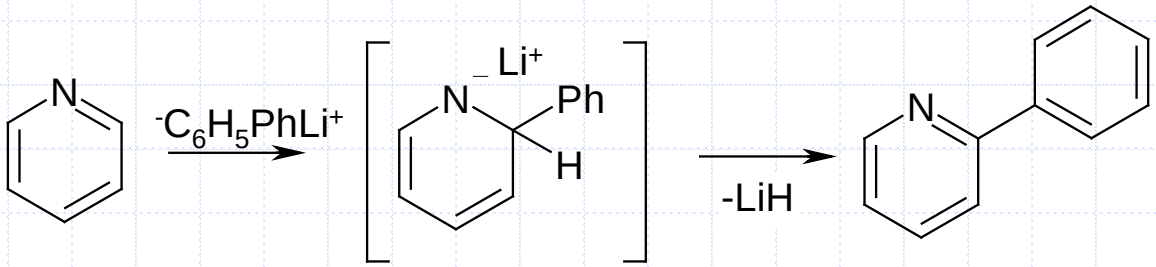
kinolin

Reaktivnost piridinov: SN_{Ar}

Čičibabin-ova reakcija: aminiranje na o-mestu z natrijevim amidom

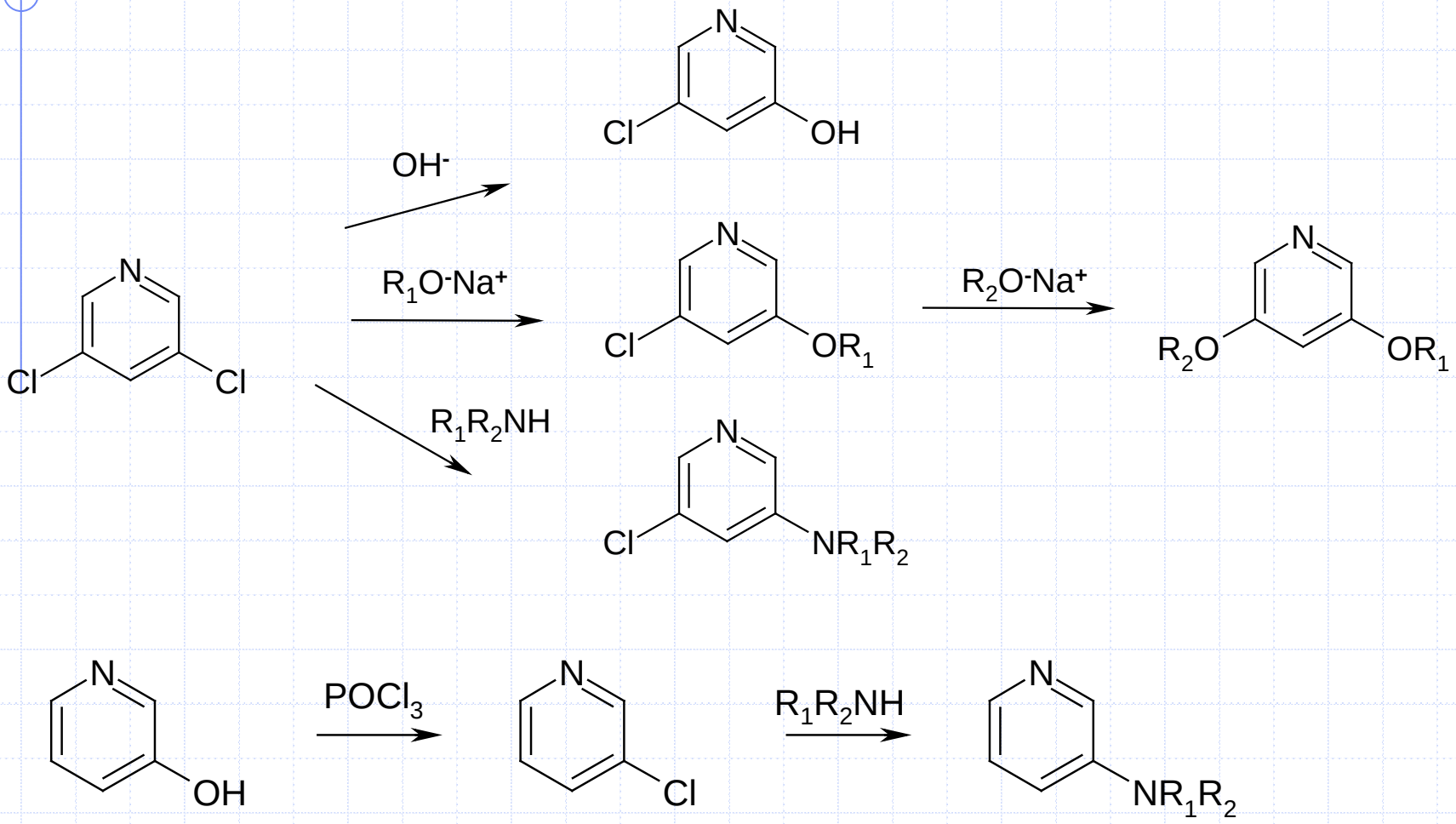


Analogno: reakcija s fenil litijem



Nukleofilne aromatske substitucije

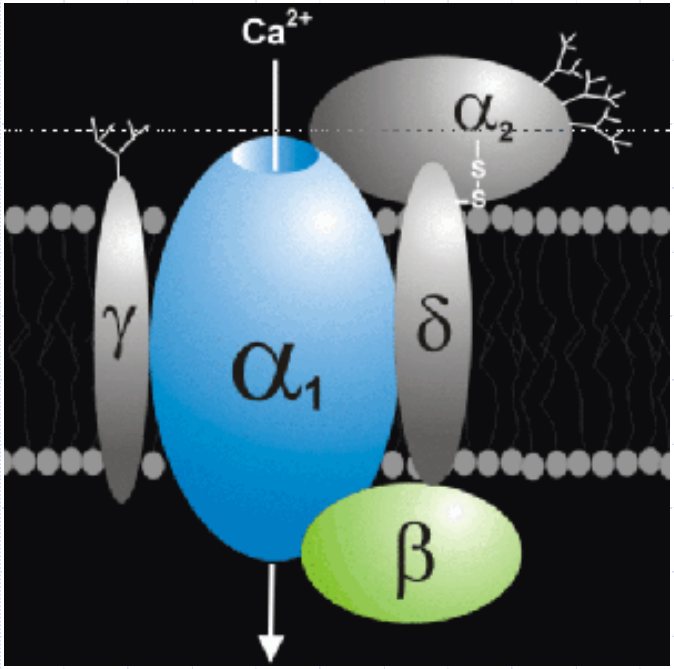
potekajo lažje kot pri benzenu



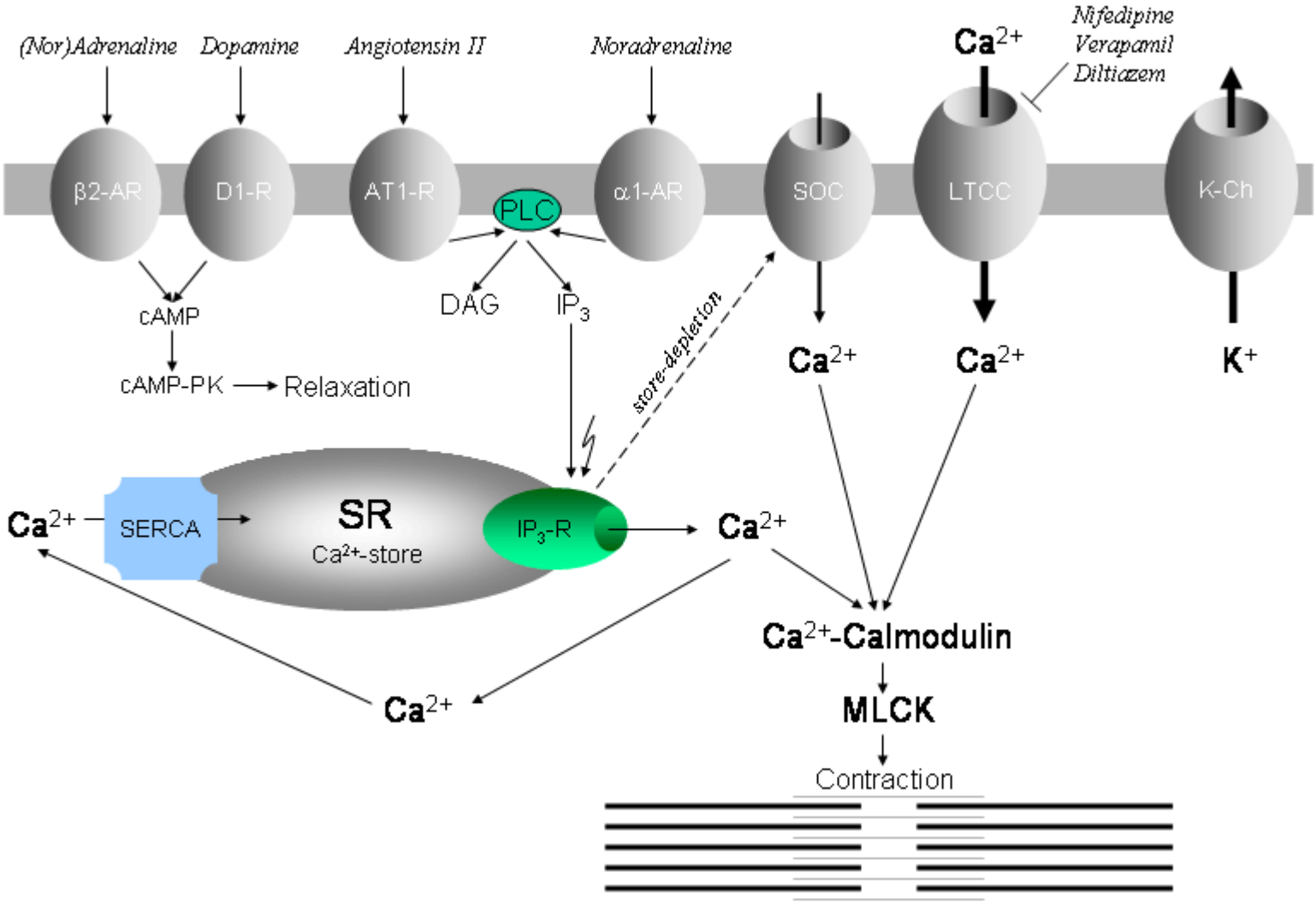
Ca antagonisti

- SKRIPTA

- mehanizem delovanja
- skupine kalcijevih antagonistov
- metabolizem
- odnos med strukturo in delovanjem pri dihidropiridinski skupini



Ca antagonisti



Ca antagonisti

- ***Simplified view of the pharmacological action of L-type Ca2+ channel blockers in arterial smooth muscle:*** *In contrast to cardiomyocytes action potentials are not carried by fast sodium channels in smooth muscle and depolarzations are more long lasting. Contraction requires the binding of Ca2+ to calmodulin, which then activates myosin light chain kinase (MLCK). MLCK phosphorylates the light chain of myosin which turns on contraction. The Ca2+ for activation of this pathway can enter through L-type Ca2+ channels in response to depolarization. Ca2+ channel blockers inhibit this pathway through concentration-dependent block of Ca2+ entry. Alternatively, Ca2+ can be released from intracellular stores after activation of membrane receptors (e.g. of angiotensin II AT1 or a1 -adrenergic receptors) coupled to IP3 production. IP3 opens IP3 receptor channels, RyR related Ca2+ release channels in the SR. This process does not involve L-type Ca2+ channels and is not inhibited by Ca2+ channel blockers. Store-depletion also triggers the activation of "store-operated channels" (SOC) in the plasma membrane which are also not sensitive to Ca2+ channel blockers. Receptor-mediated activation of cAMP-dependent protein kinase (cAMP-PK) results in muscle relaxation through different mechanisms. D1-R, dopamine1 receptor; AR, adrenergic receptor; PLC, phospholipase C.*

Sintezne naloge

- Sinteza NIKARDIPINA

  3-{2-[benzil(metil)amino]etil}-5-metil-2,6-dimetil-4-(3-nitrofenil)-1,4-dihidro-3,5-piridindikarboksilat

  Iz metilacetoacetata, amoniaka in 2-[benzil(metil)amino]etil-3-oksobutanoata

- Sinteza NIFEDIPINA

  dimetil 2,6-dimetil-4-(2-nitrofenil)-1,4-dihidro-3,5-piridindikarboksilat

  Iz metil 3-oksobutanoata, amoniaka in 2-nitrobenzaldehida

Sintezne naloge

- Sinteza VERAPAMILA

  4-[(3,4-dimetoksifenetil)metilamino]-1-(3,4-dimetoksifenil)-1-izopropil-butilcianid

  Iz 1-(3,4-dimetoksifenil)benzilcianida, 1-bromo-3-kloropropana in N-[2-(3,4-dimetoksifenil)etil]-N-metilamina

Naloga za točko