

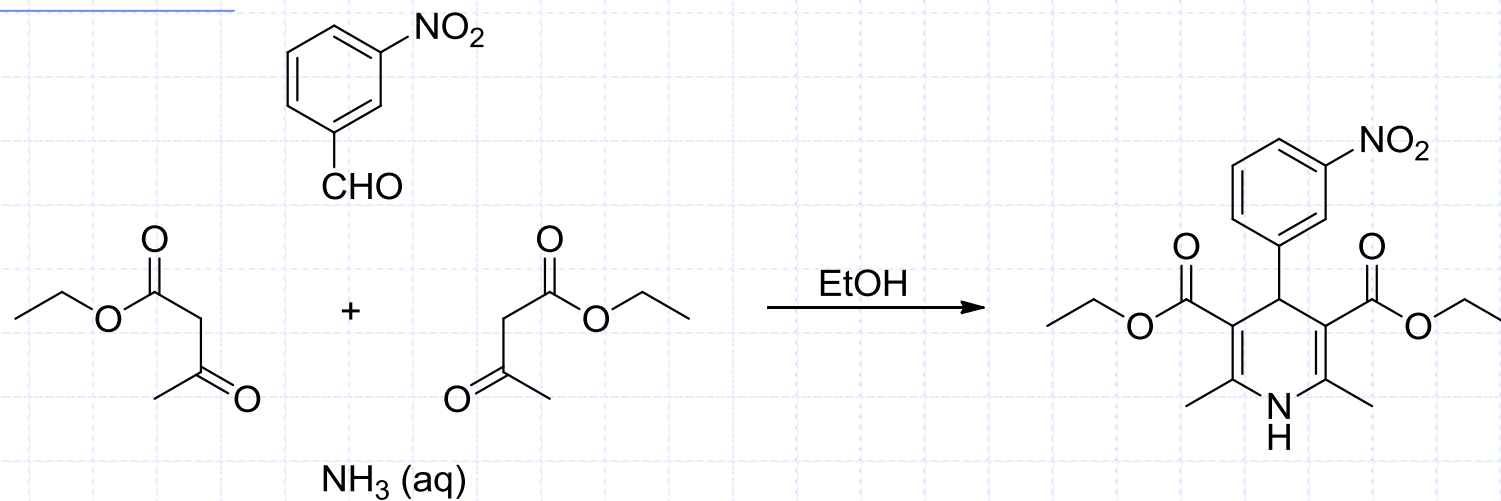


Katedra za farmacevtsko kemijo

Sinteza metanifedipina

9. vaja

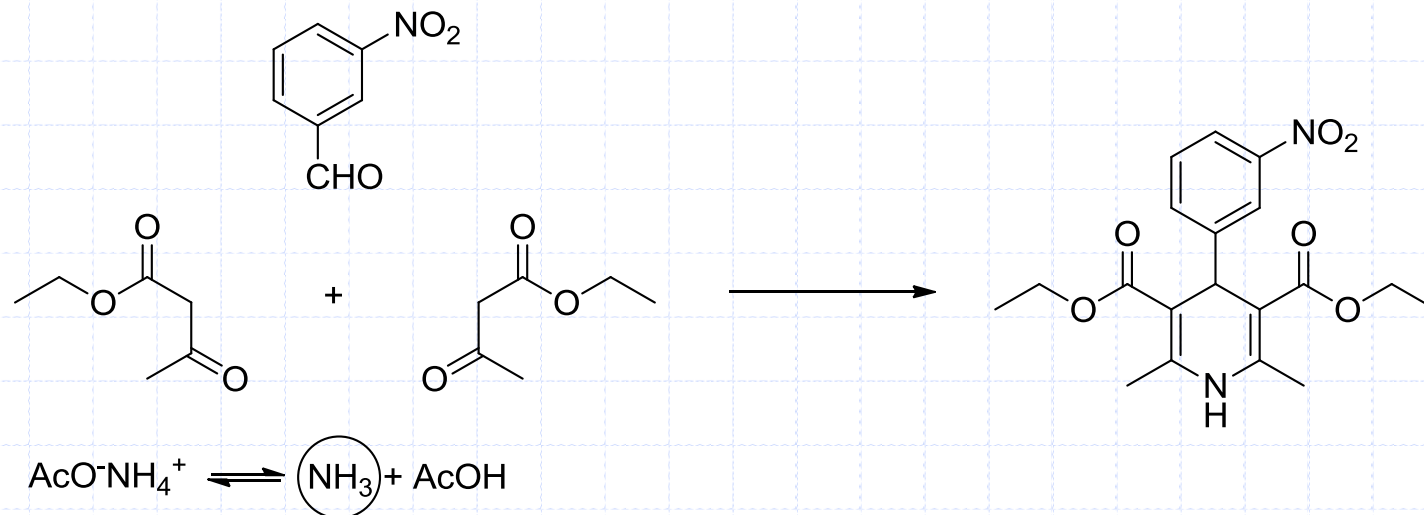
Sinteza metanifedipina



- ◆ Hantzscheva sinteza 1,4-dihidropiridinov
- ◆ kondenzacija dveh molov β -ketoestra z aldehydom in amoniakom

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

Alternativna sinteza

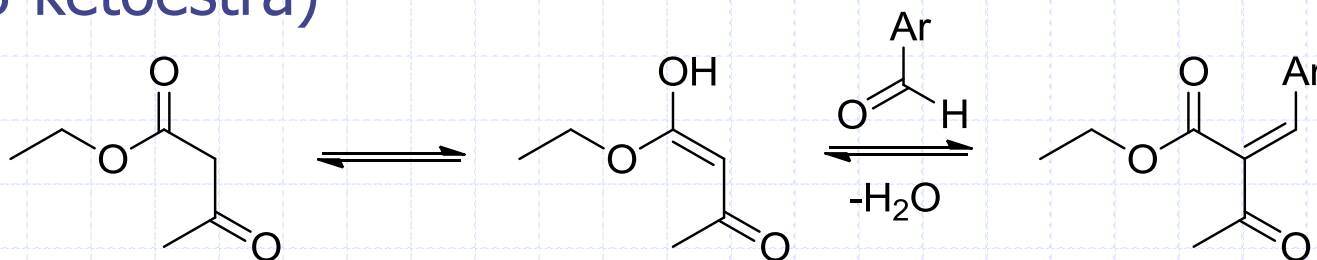


◆ sinteza z ultrazvokom

- ◆ Predlagajte orositveni reagent za detekcijo poteka reakcije.
- ◆ Zakaj pri alternativni sintezi dodamo amonijev acetat?
- ◆ Kako se v obeh primerih znebimo prebitnega etilacetoacetata?

Mehanizem reakcije

1. Knoevenaglova kondenzacija (aldehid + 1 ekvivalent β -ketoestra)

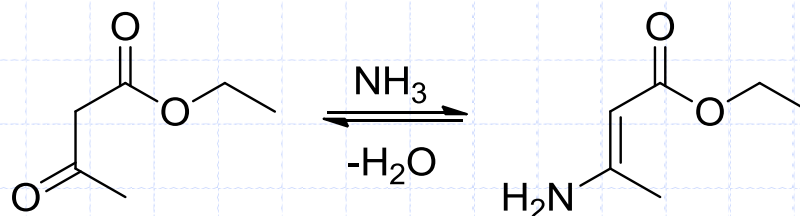


- ◆ kondenzacija med aldehidi ali ketoni in spojinami z aktivirano metilensko skupino
- ◆ produkti: α,β -nenasičene spojine
- ◆ katalizator: baza

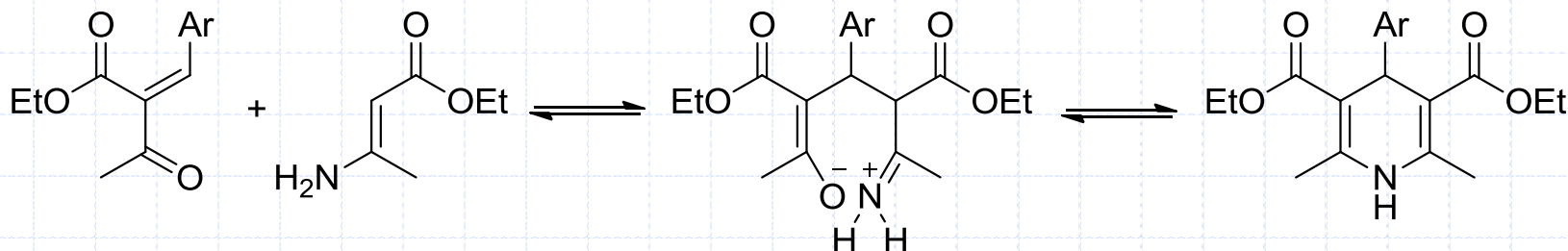
<http://www.organic-chemistry.org/namedreactions/knoevenagel-condensation.shtm>

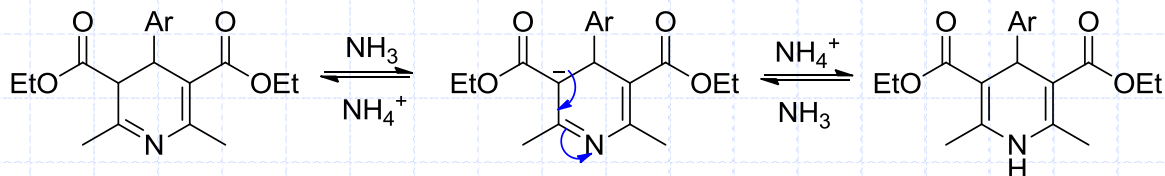
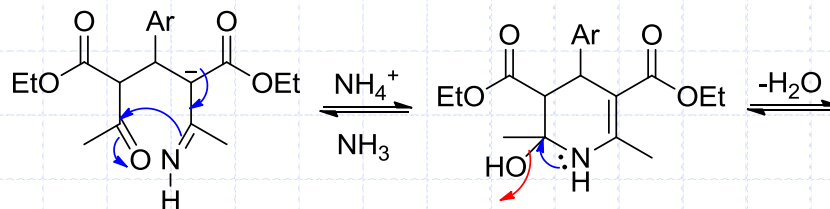
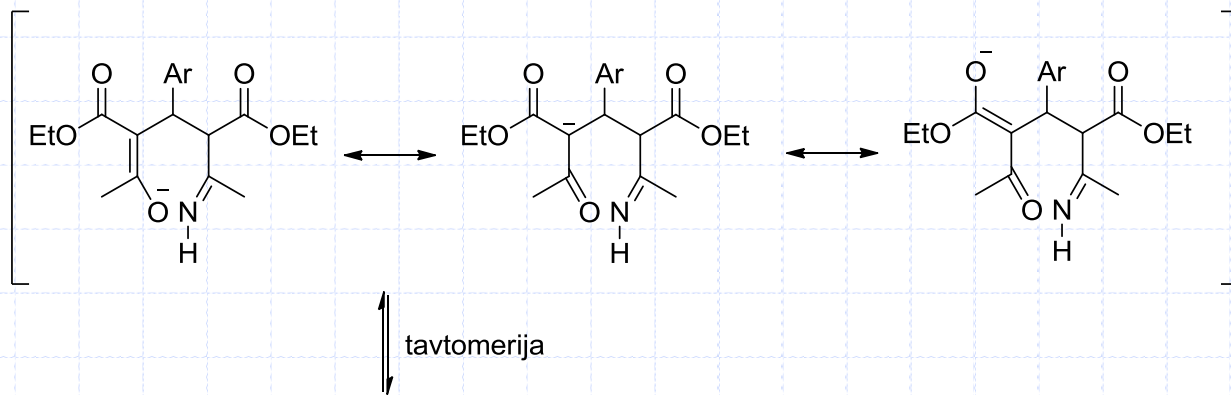
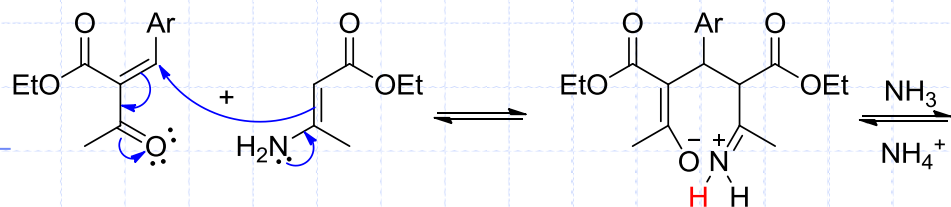
Mehanizem reakcije

2. Sinteza enamin-estra (amoniak + 1 ekvivalent β -ketoestra)



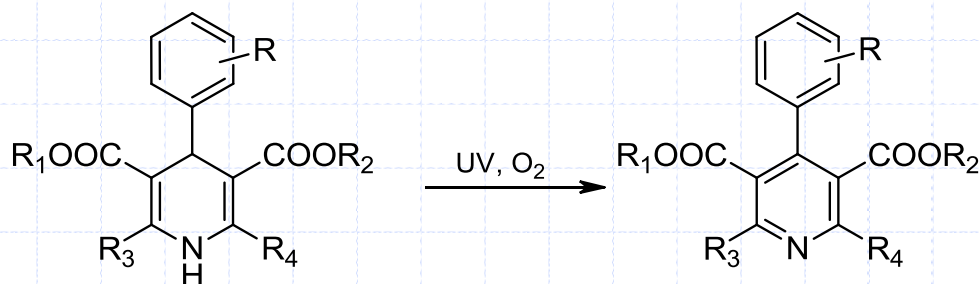
3. Zaporedni kondenzaciji med intermediatoma do dihidropiridina





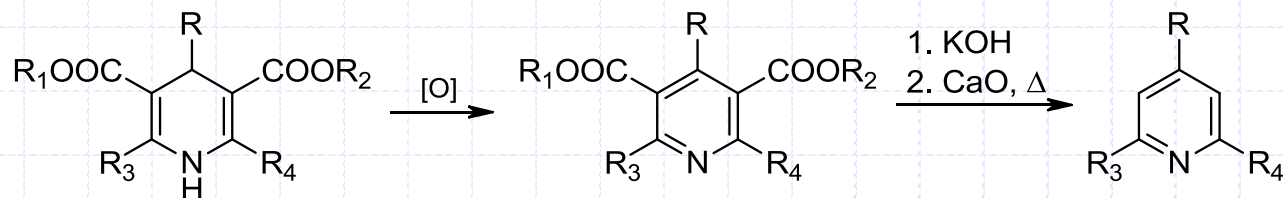
Lastnosti 1,4-dihidropiridinov

Občutljivi na oksidante: oksidacija do piridinov



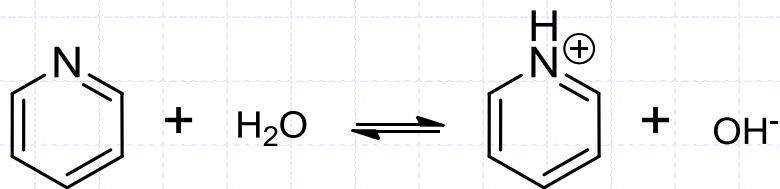
Učinkovine zaščitene
pred svetlobo!

Sinteza piridinov

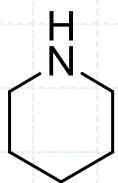


Lastnosti piridinov

šibka baza:



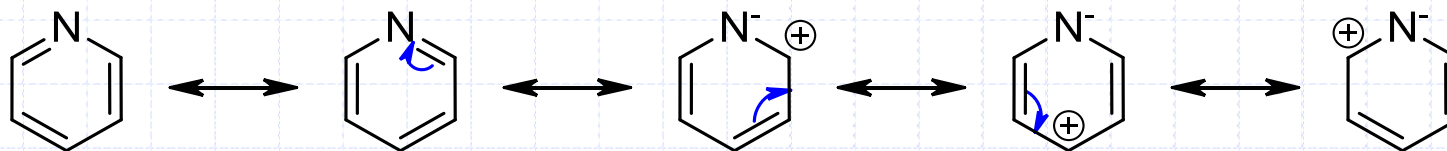
$$\text{pK}_a = 5,2 \quad (\text{pK}_b = 8,8)$$



$$\text{pK}_a = 11,1 \quad (\text{pK}_b = 2,9)$$

Reaktivnost piridinov

- manjša elektronska gostota obročnih C zaradi prisotnosti bolj elektronprivlačnega N atoma

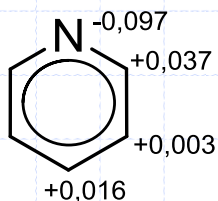


⇒ manjša reaktivnost za elektrofilne aromatske substitucije

⇒ SE_{Ar} potekajo na *m*-mesto

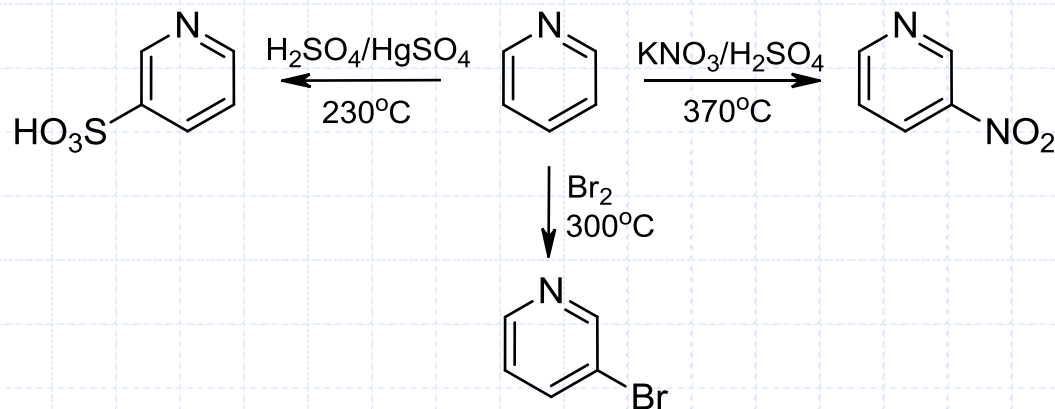
⇒ bolj občutljiv za nukleofile

⇒ SN_{Ar} potekajo na *o*- in *p*-mesto

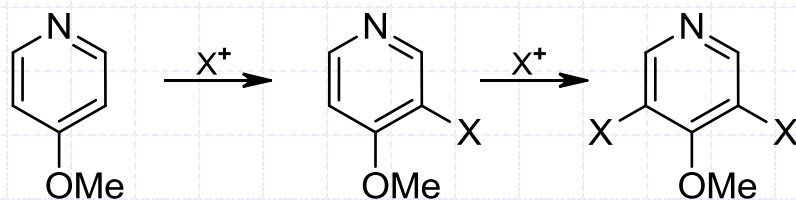


Reaktivnost piridinov - SE_{Ar}

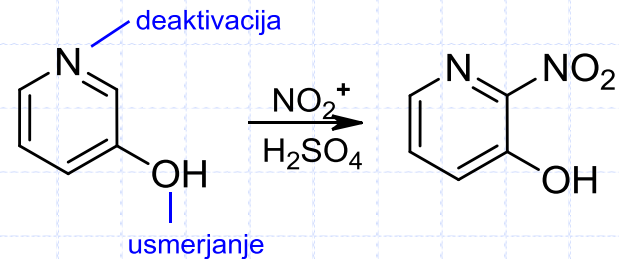
◆ potekajo zgolj pod zelo ostrimi reakcijskimi pogoji



◆ skupine, ki aktivirajo za SE_{Ar} :

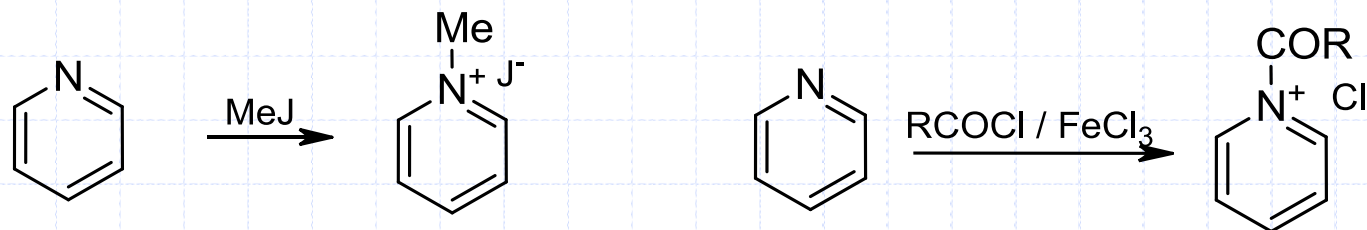


$X = Cl, Br, NO_2, SO_3H$

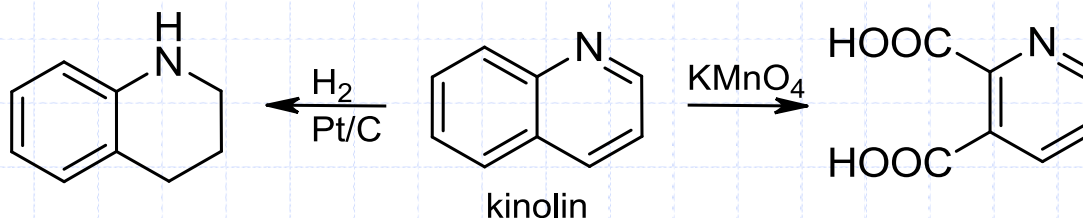


Reaktivnost piridinov

- ◆ Friedel-Crafts-ove alkiliranje in aciliranje poteče na obročni N-atom → nastanejo piridinijeve soli

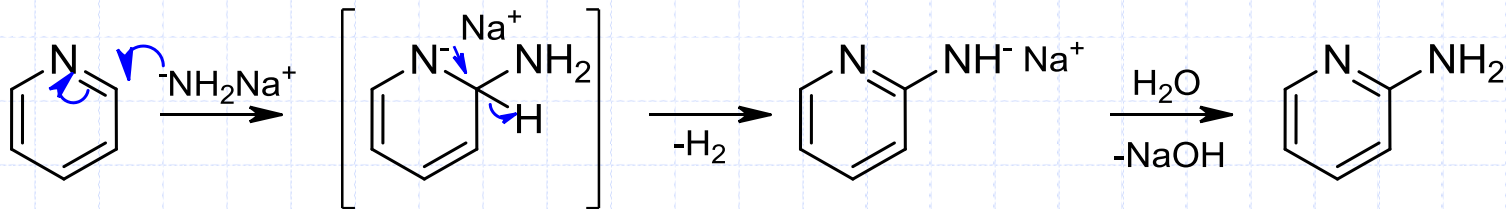


- ◆ piridin je bolj obstojen napram oksidacijam kot benzen, lažje pa ga reduciramo (velja za vse heteroaromate)

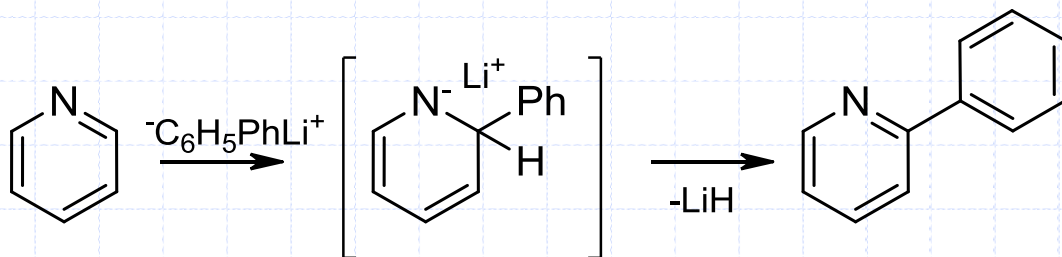


Reaktivnost piridinov - S_N_{Ar}

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

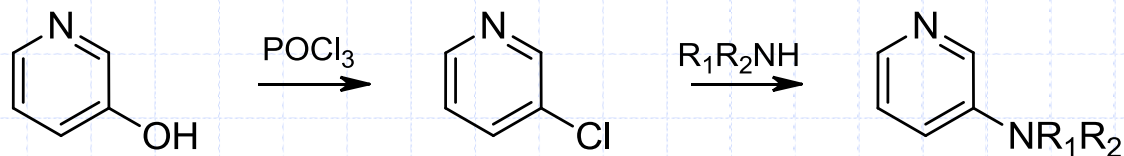
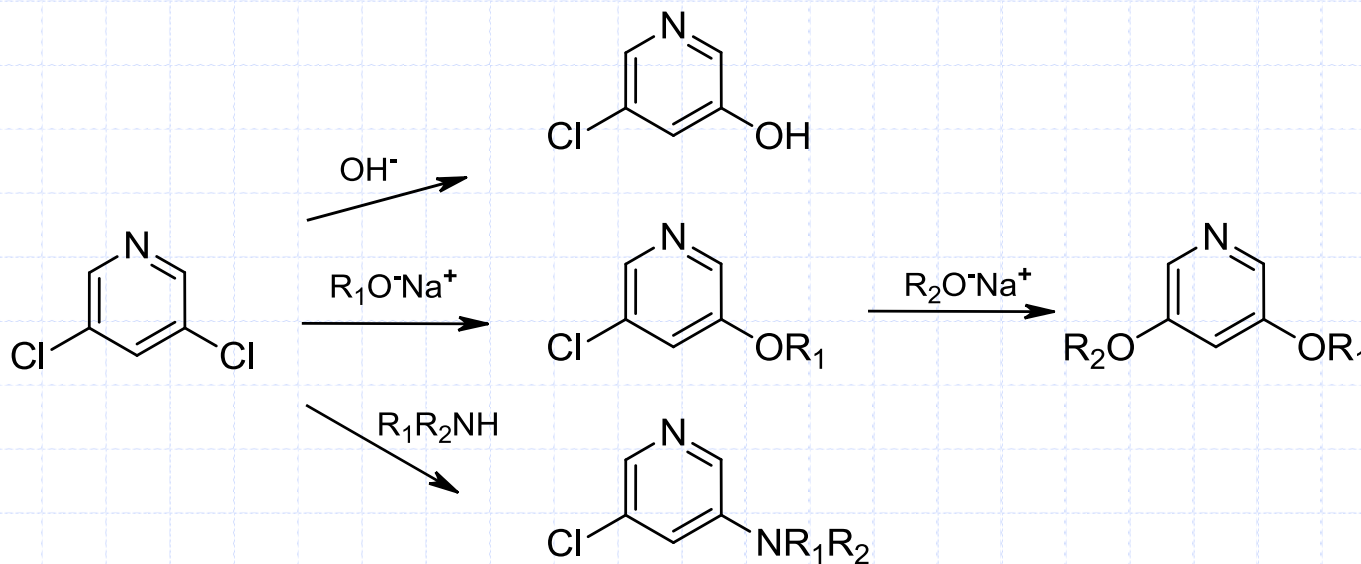


Analogno: reakcija s fenil litijem



Reaktivnost piridinov - S_N_{Ar}

- potekajo lažje kot pri benzenu



Sintezne naloge

◆ Sinteza NIKARDIPINA

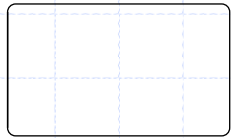
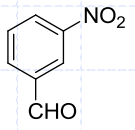
3-{2-[benzil(metil)amino]etil}-5-metil-2,6-dimetil-4-(3-nitrofenil)-1,4-dihidro-3,5-piridindikarboksilat

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

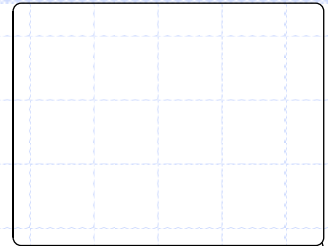
◆ Sinteza NIFEDIPINA

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

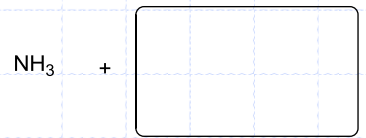
Iz metil 3-oksobutanoata, amoniaka in 2-nitrobenzaldehyda



A



A ime rkc.



B

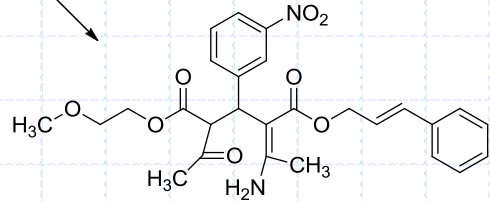


B ime rkc.

+

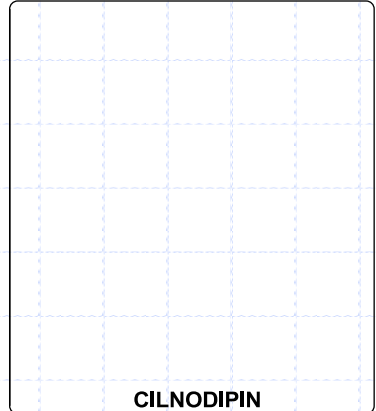
C ime rkc.

C



D ime rkc.

D -H₂O



Sintezne naloge

◆ Sinteza VERAPAMILA

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

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