TÁMOP-4.1.1.F-14/1/KONV-2015-0006
SZTE TTIK, KTCS, 1a) Duális és moduláris képzésfejlesztés a mesterképzéshez

Aromás heterociklusok kémiája

Pálinkó István, egyetemi tanár

SZÉCHENYI 2020
MAGYARORSZÁG KORMÁNYA
Európai Unió
Európai Szociális Alap
BEFEKTETÉS A JÖVŐBE

miért muszáj ezzel a vegyületcsaláddal foglalkozni?

azért, mert ilyen vegyületekkel van telis-teli az egész élővilág

meg akarjuk ismerni szerepüket

bele akarunk nyúlni az élő rendszerekbe,
pl. gyógyítani akarunk betegségeket, kártevőket akarunk elpusztítani, stb.

mit kell mindezért tennünk?

meg kell ismernünk szerkezetüket, főbb reakcióikat

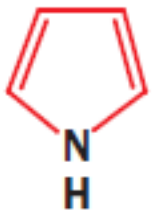
és a főbb gyűrűelőállítási módszereket

nehéz lesz?

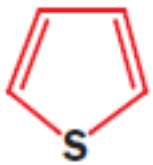
igen, mert kaotikusnak látszik, de lehet bele rendszert vinni

a fontosabb alapszerkezetek és aromás jellegük

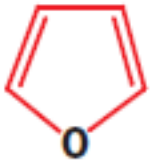
öttagú egy heteroatomot tartalmazó alapvegyületek



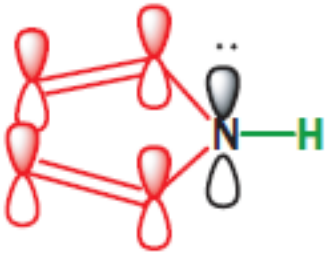
pyrrole



thiophene



furan



pK_a
ca. 35

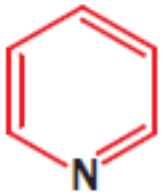
pK_a
16.5

pK_a
ca. 35

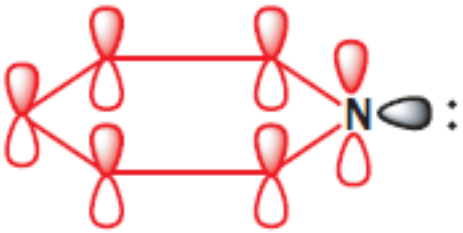
aromás rezonancia stabilizációs energia

(benzol: ~152 kJ/mol)
tiofén: ~122 kJ/mol
pirrol: ~90 kJ/mol
furán: ~68 kJ/mol

hattagú egy nitrogénatomot tartalmazó alapvegyület



pyridine



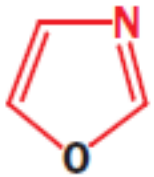
lone pair in sp^2 orbital at
right angles to p orbitals in ring:
no interaction between
orthogonal orbitals

aromás rezonancia stabilizációs energia

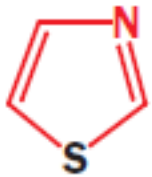
(benzol: ~152 kJ/mol)
piridin: ~117 kJ/mol

azolok

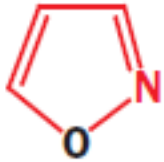
öttagú egy nitrogént és egy oxigént vagy kenet tartalmazó heterociklusok



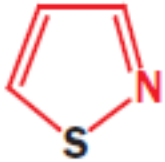
oxazole



thiazole



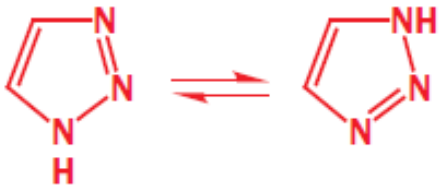
isoxazole



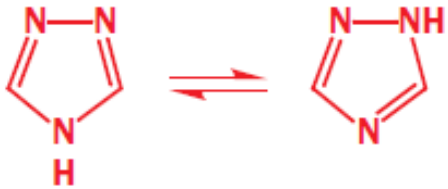
isothiazole

öttagú két vagy több nitrogénatomot tartalmazó heterociklusok

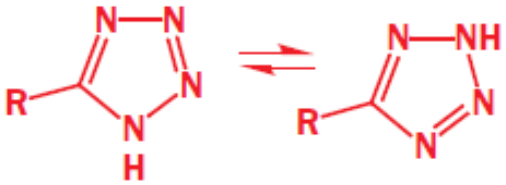
two identical tautomers of imidazole



1,2,3-triazole



1,2,4-triazole

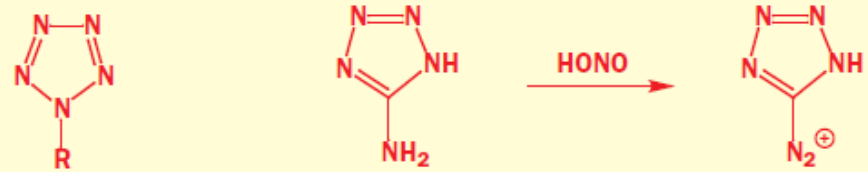


two tautomers of tetrazole

a pentazole
highly explosive!

Nitrogen atoms and explosions

Compounds with even two or three nitrogen atoms joined together, such as diazomethane (CH_2N_2) or azides (RN_3), are potentially explosive because they can suddenly give off stable gaseous nitrogen. Compounds with more nitrogen atoms, such as tetrazoles, are likely to be more dangerous and few people have attempted to prepare pentazoles. The limit is reached with diazotetrazole, with the amazing formula CN_6! It is made by diazotization of 5-aminotetrazole, which first gives a diazonium salt.

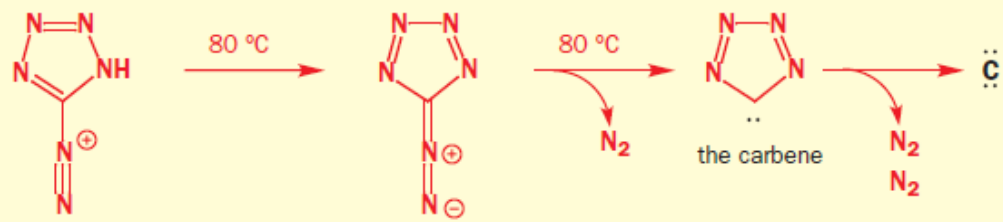


a pentazole
highly explosive!

5-amino-(1H)-tetrazole

the diazonium salt
highly explosive!

The diazonium salt is extremely dangerous: 'It should be emphasised that [the diazonium salt] is extremely explosive and should be handled with great care. We recommend that no more than 0.75 mmol be isolated at one time. Ethereal solutions are somewhat more stable but explosions have occurred after standing at –70 °C for 1 hr.' So much for that, but what about the diazo compound? It is extremely unstable and decomposes to a carbene with loss of one molecule of nitrogen and then loses two more to give...



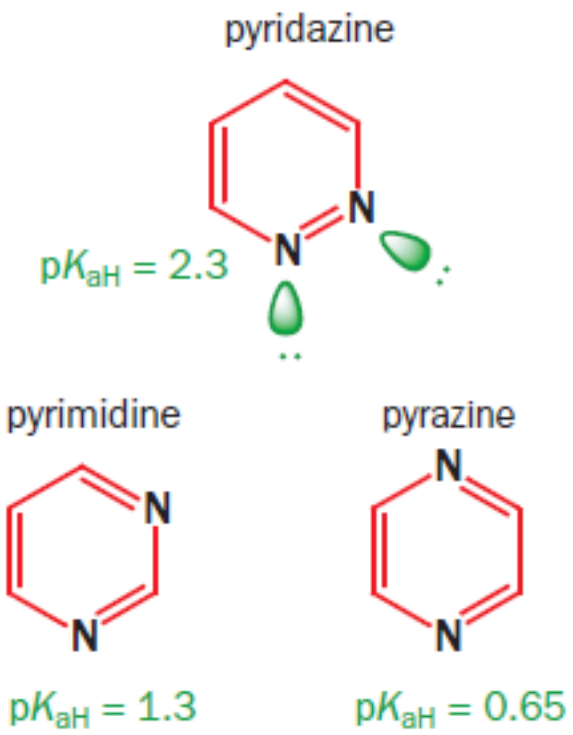
the diazonium salt
highly explosive!

the diazo compound
highly explosive!

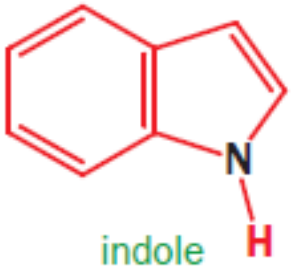
All that is left is a carbon atom and this is one of very few ways to make carbon atoms chemically. The carbon atoms have remarkable reactions and these have been briefly studied, but the hazardous preparation of the starting materials discourages too much research. However, you will see in the next chapter that 1-amino tetrazole is a useful starting material for making an anti-allergic drug.

azinok

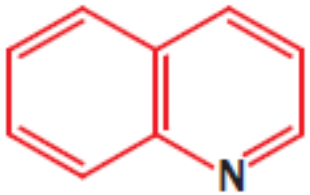
hattagú két nitrogénatomot tartalmazó heterociklusok



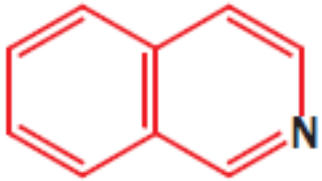
kondenzált gyűrűs heterociklusok



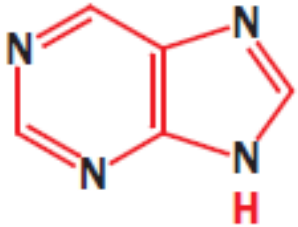
indole



quinoline



isoquinoline



purine

Reakciók

aromás elektrofil szubsztitúció

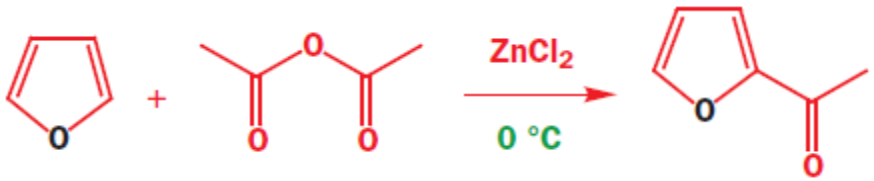
aromás nukleofil szubsztitúció

metallálási reakciók (a heteroatomon,
de méginkább a gyűrű valamelyik szénatomján)

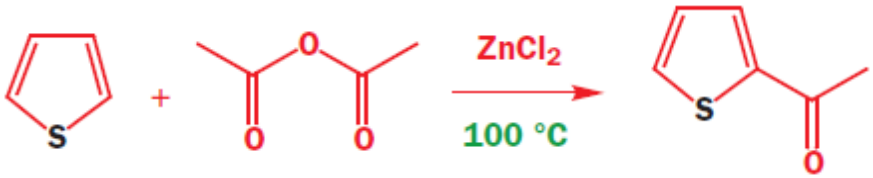
cikloaddíció

az öttagú egy heteroatomot tartalmazó gyűrűk jellemző reakciója az aromás elektrofil szubsztitúció

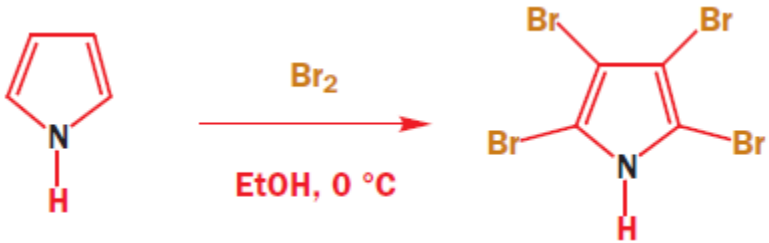
általában jól megy (jobban mint a benzol esetén)



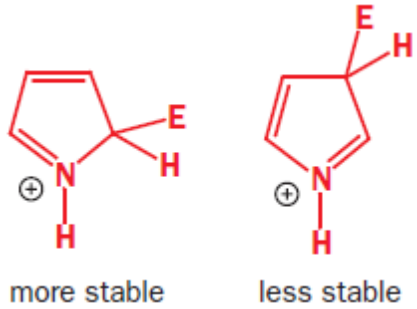
néha kicsit küzdeni kell (főként a tiofén esetén – ez hasonlít legjobban a benzolhoz)

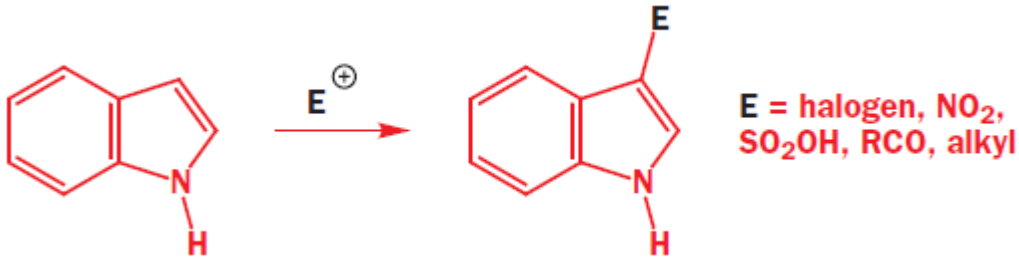


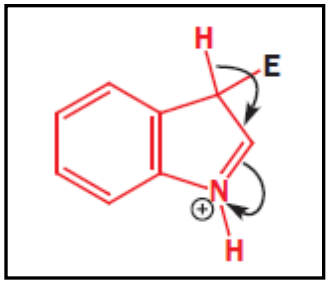
néha egyenesen túl jól megy

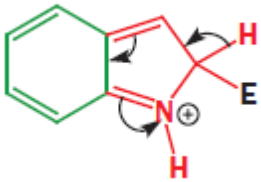


a pirrol és az indol aromás elektrofil szubsztitúciója – irányítási szabályok







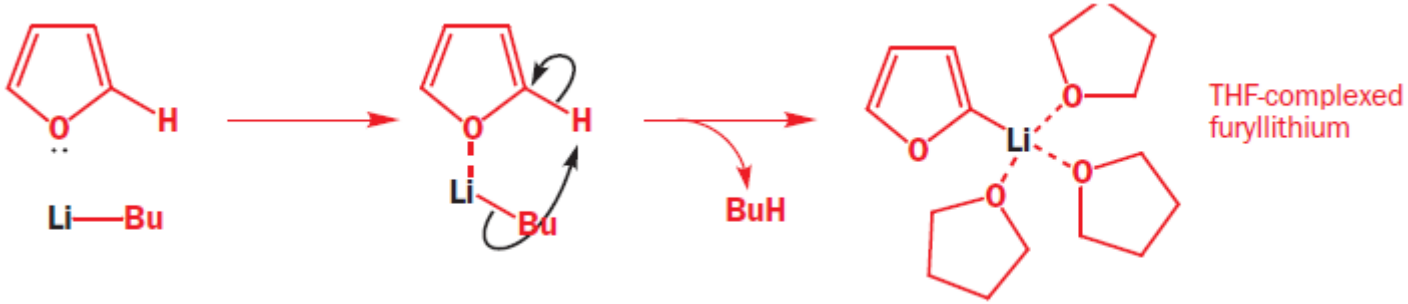


megmarad a másik gyűrű aromás szerkezete

az aromás nukleofil szubsztitúció nem jellemző,

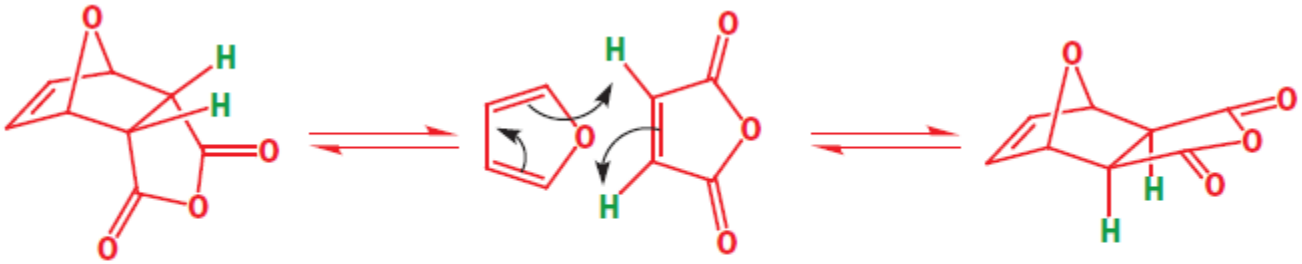
metallálás – C-metallálás

mechanizmus



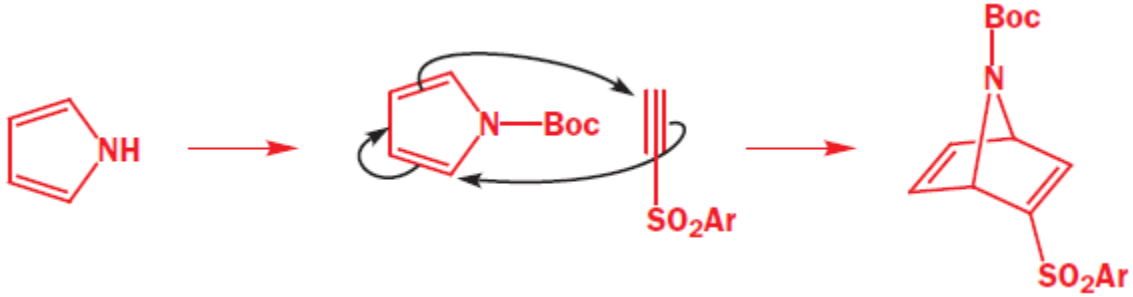
orto-irányított lítiálás

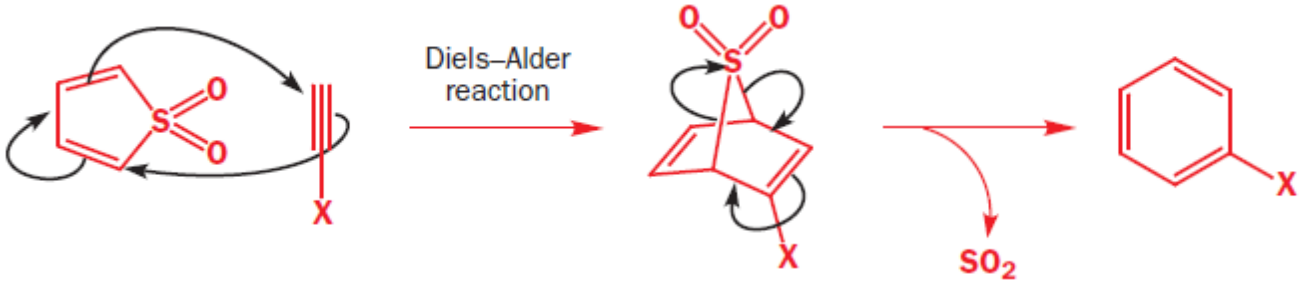
öttagú egy heteroatomos aromás vegyületek Diels-Alder reakciói



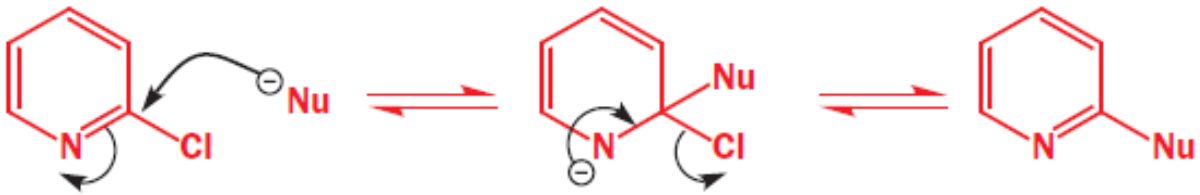
kinetically preferred
endo adduct

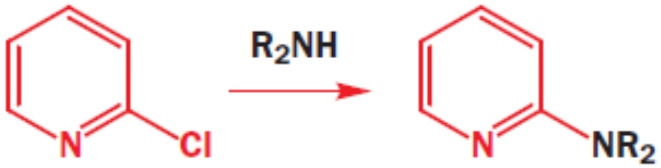
thermodynamically preferred
exo adduct

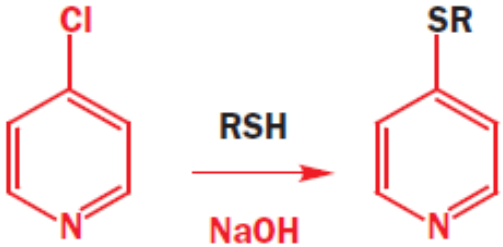


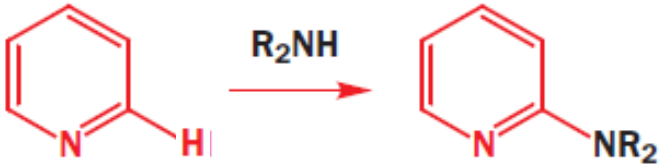


a hattagú egy heteroatomot tartalmazó gyűrűk jellemző reakciója az aromás nukleofil szubsztitúció



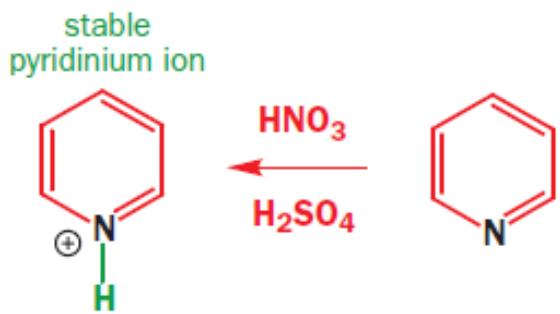


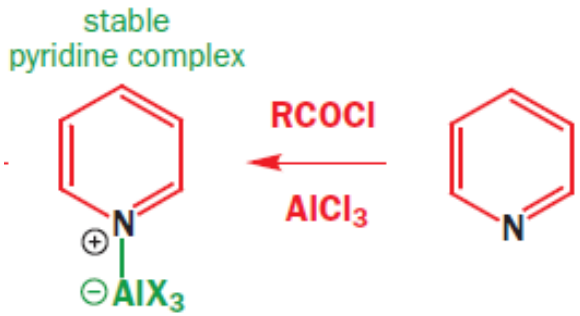




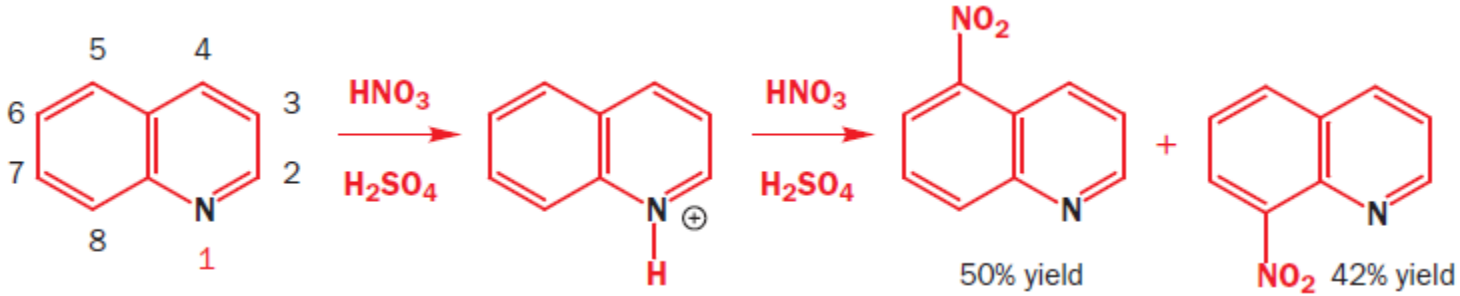
H^--ion (!) távozik (Csicsibabin-reakció)

az elektrofil szubsztitúció nem jellemző, csak goromba körülmények között megy, de a Friedel-Crafts reakciók még úgy sem





a nitrálószer az acetilnitrát (CH_3COONO_2)

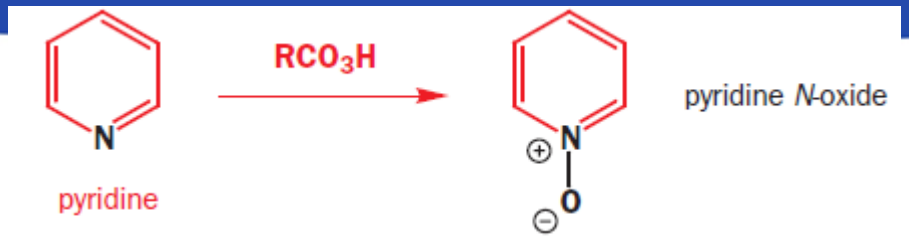


általában N-metallálás történik, C-metallálás csak akkor, ha a nitrogénatomot védjük

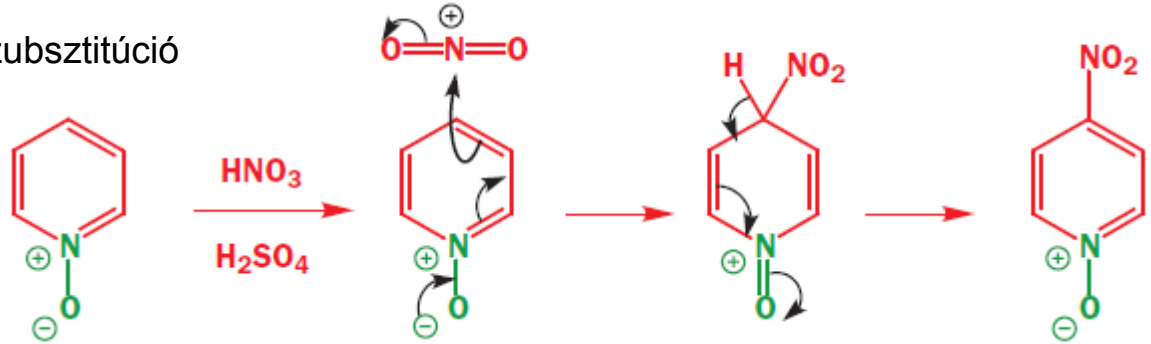
a piridingyűrű túl aromás ahhoz, hogy direkt módon részt vegyen Diels-Alder reakcióban

a piridin N-oxid aktív mind aromás elektrofil, mind aromás nukleofil szubsztitúciós reakciókban

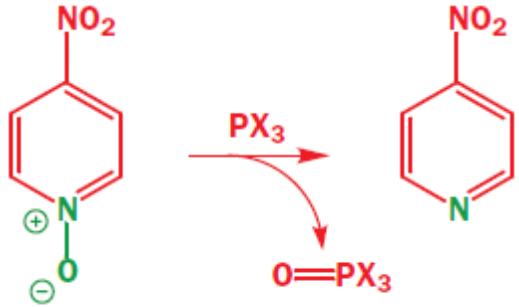
előállítás



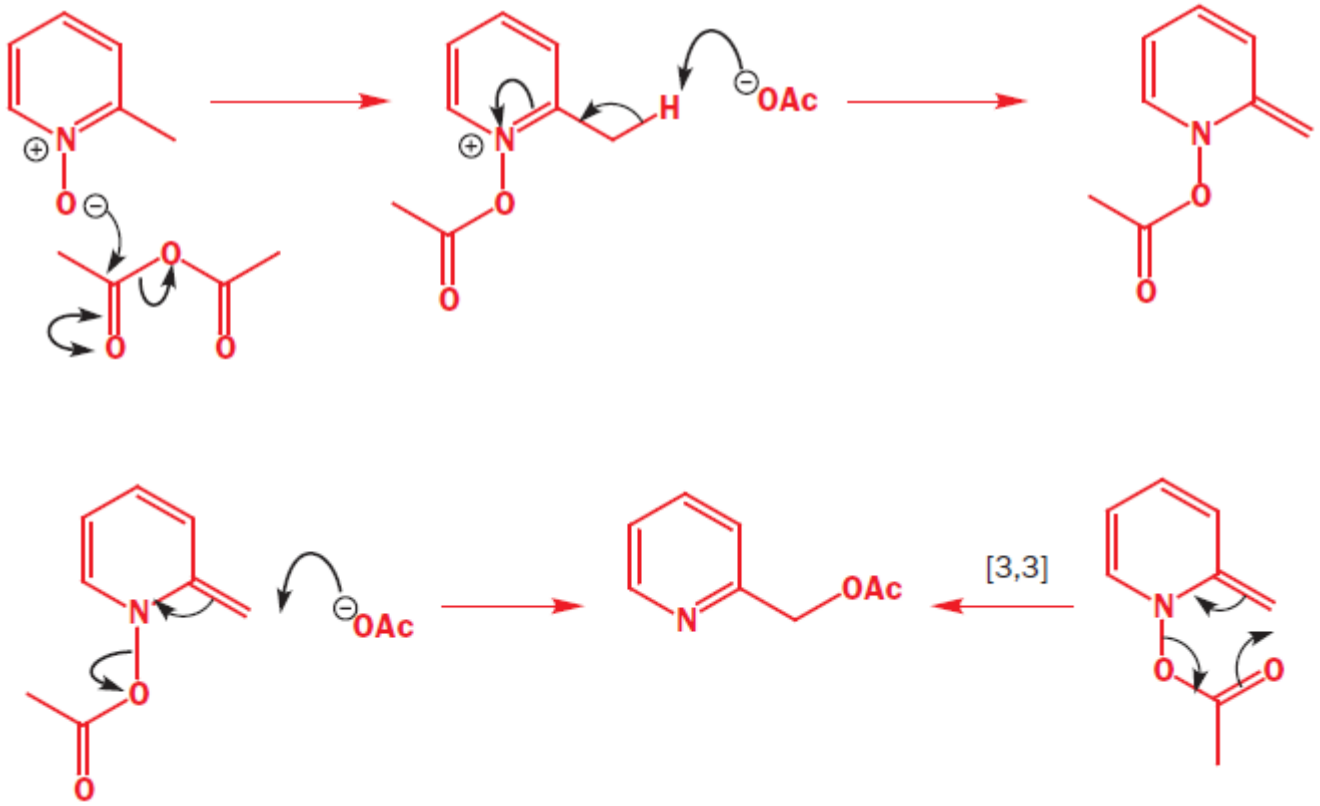
aromás elektrofil szubsztitúció



az N-oxid redukciója



aromás nukleofil szubsztitúció



Heteroaromás gyűrűk előállítása

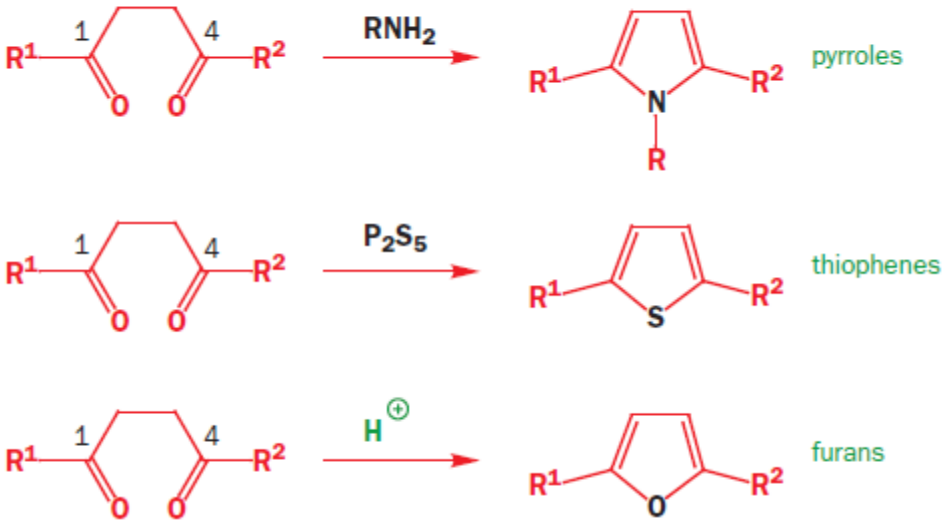
Ring construction by ionic cyclization

Heterocycles with one heteroatom

five-membered rings

pyrroles, thiophenes, and furans

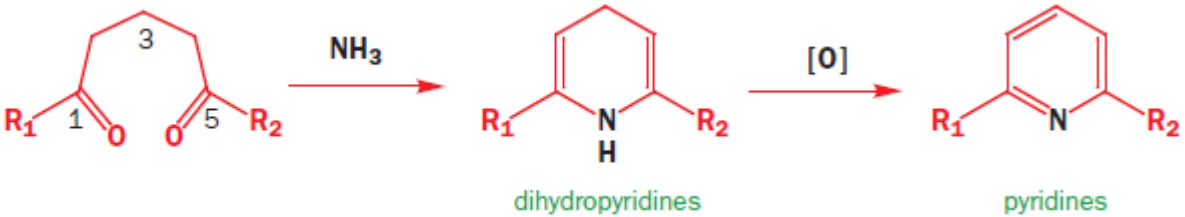
ideally made by this strategy
from 1,4-dicarbonyl compounds



six-membered rings

pyridines

made by this strategy
from 1,5-dicarbonyl
compounds with oxidation

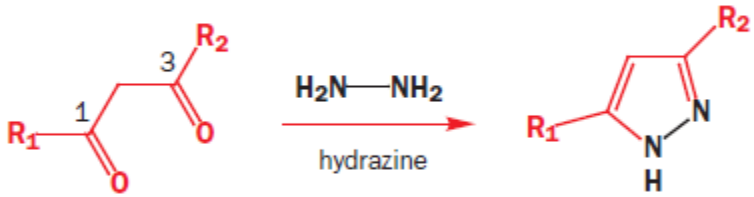


Heterocycles with two adjacent heteroatoms

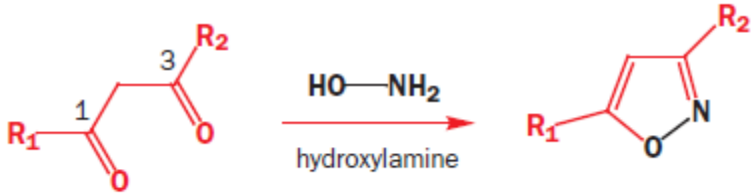
five-membered rings

pyrazoles and isoxazoles

ideally made by this strategy from 1,3-dicarbonyl compounds

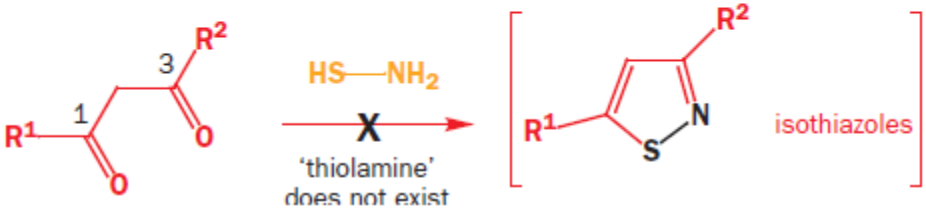


pyrazoles



isoxazoles

Note. This strategy is *not* suitable for isothiazoles as 'thiolamine' does not exist

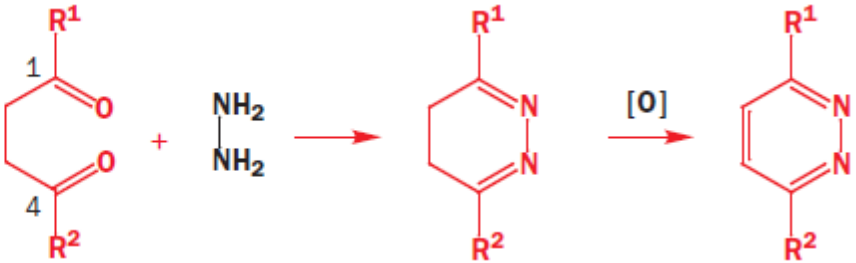


isothiazoles

six-membered rings

pyridazines

ideally made by this strategy from 1,4-dicarbonyl compounds with oxidation



Heterocycles with two non-adjacent heteroatoms

five-membered rings

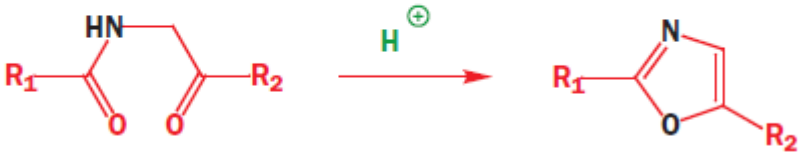
imidazoles and thiazoles

ideally made by this strategy from α-halocarbonyl compound

a thiazole

an imidazole

Note. This strategy is *not* suitable for oxazoles as amides are not usually reactive enough: cyclization of acylated carbonyl compounds is usually preferred

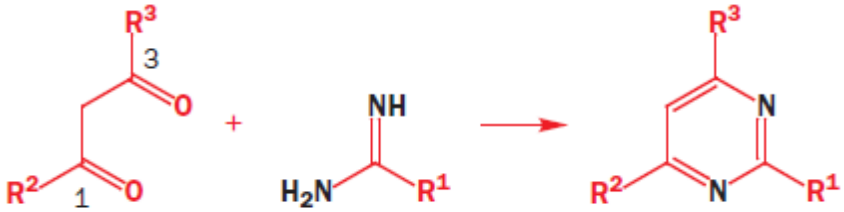


an oxazole

six-membered rings

pyrimidines

ideally made by this strategy from 1,3-dicarbonyl compounds



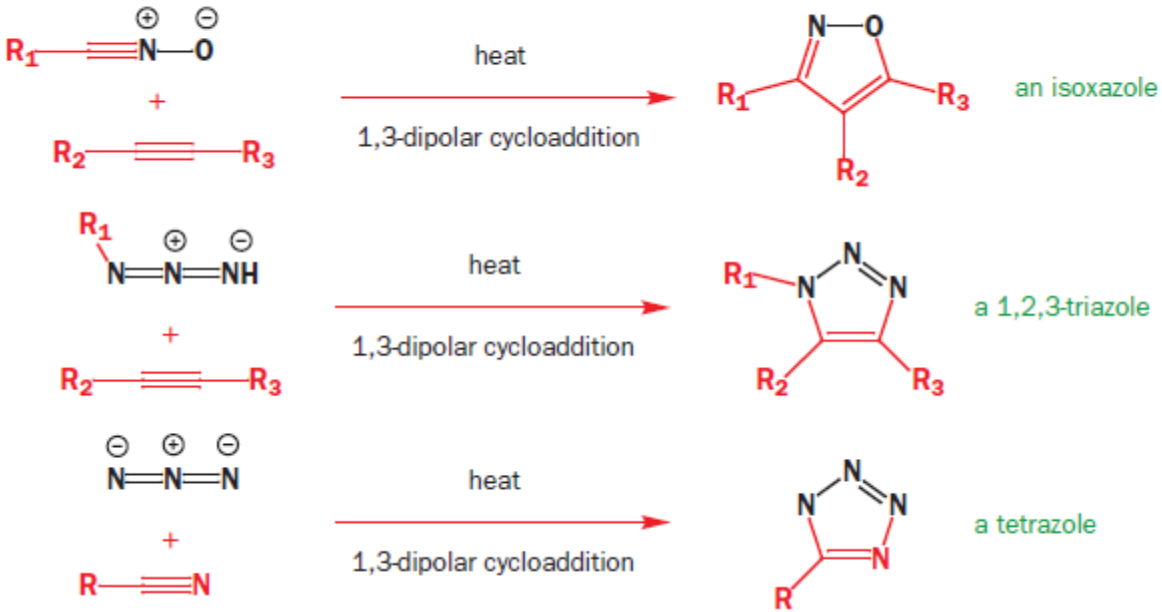
an amidine

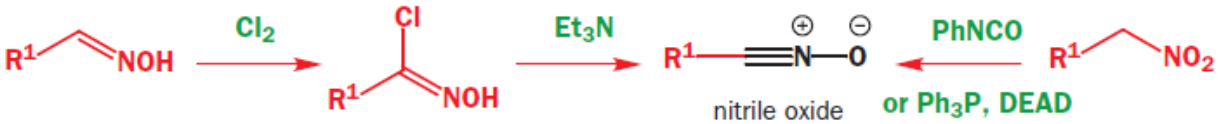
a pyrimidine

Ring construction by pericyclic reactions

Cycloaddition reactions

1,3-dipolar cycloaddition is ideal for the construction of isoxazoles, 1,2,3-triazoles, and tetrazoles

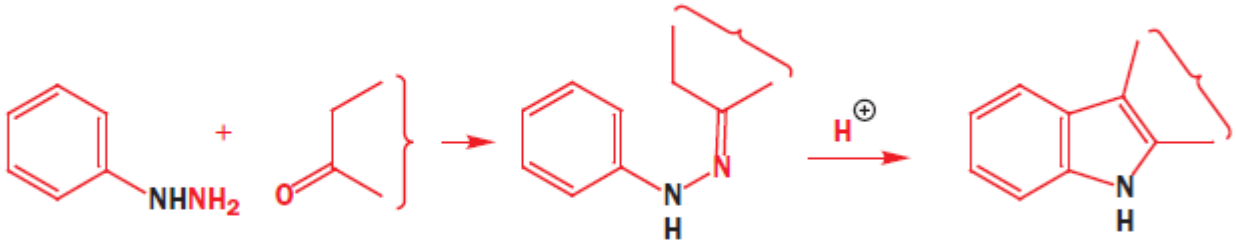




in situ állítják elő

Sigmatropic rearrangements

a special reaction that is the vital step of the Fischer indole synthesis

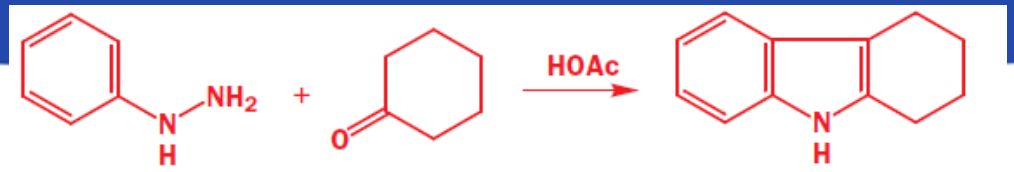


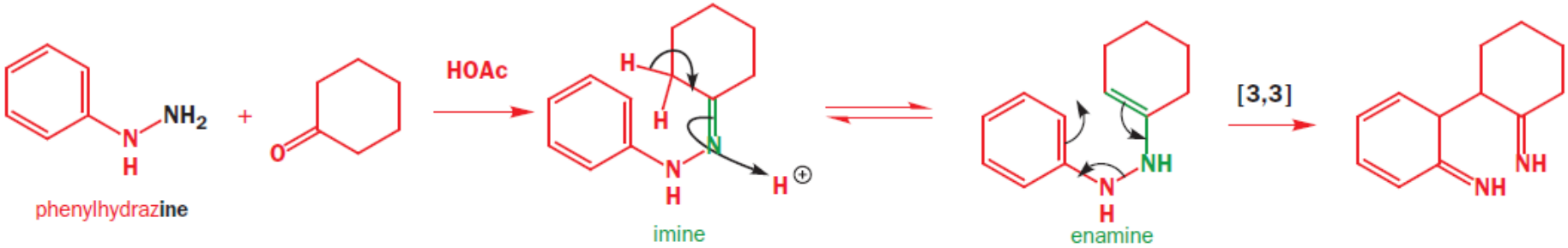
phenylhydrazine

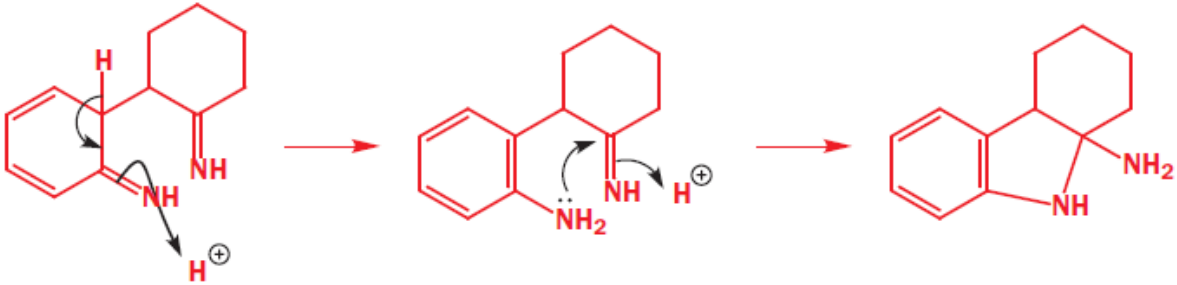
a phenylhydrazone

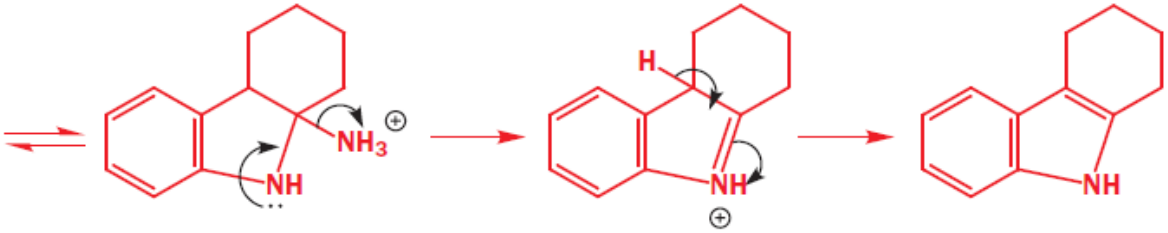
an indole

példareakció és mechanizmus (Fischer-féle indolszintézis)









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