UNIVERSIDAD
DE CHILE

Química Orgánica II

Unidad 3: Compuestos nitrogenados

Susan Lühr

Fundamentos en Química Orgánica

Qca. Orgánica 1
NOMENCLATURA
(nombres)

Qca. Orgánica 1
CONTRUCCIÓN
(enlaces, ángulos)

Qca. Orgánica 1
ARQUITECTURA 3D
(estereoquímica)

Qca. Orgánica 1
CARACTERÍSTICAS
(pKa, resonancia,…)

Qca. Orgánica 1/2
COMPORTAMIENTO
(reactividad: alcanos, alquenos,etc)

COMPUESTOS ORGÁNICOS

Unidad 1
REACTIVIDAD
(Cetonas y aldehídos)

Unidad 2
REACTIVIDAD
(Ác. carboxílicos)

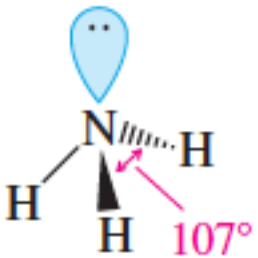
Unidad 3
REACTIVIDAD
(Nitrogenados)

Unidad 4
RECONOCIMIENTO-CARACTERIZACIÓN
(MS, IR, RMN ^{1}H, ^{13}C)

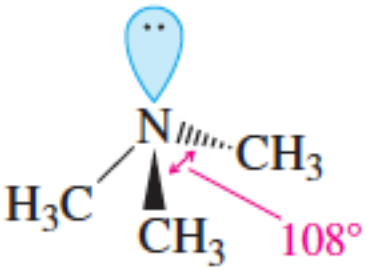
Unidad 5
MACROMOLÉCULAS
(Polímeros)

Unidad 6
MACROMOLÉCULAS
(Biomoléculas)

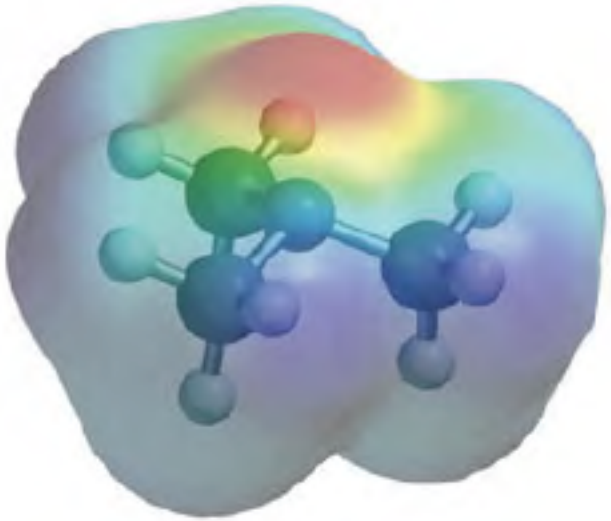
Estructuras de las aminas



ammonia

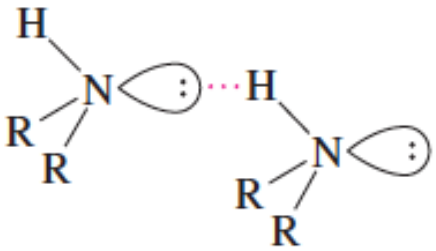


trimethylamine

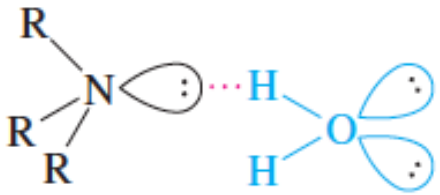


electrostatic potential
map for trimethylamine

Propiedades físicas



1° or 2° amine:
hydrogen bond donor and acceptor



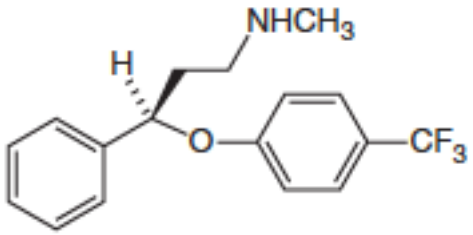
3° amine:
hydrogen bond acceptor only

TABLE 19-1 How Hydrogen Bonding Affects Boiling Points

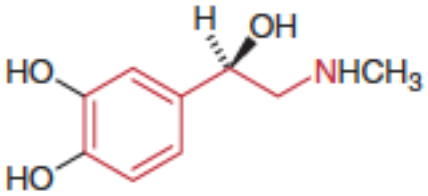
Compound	bp (°C)	Type	Molecular Weight
$(CH_3)_3N$:	3	tertiary amine	59
$CH_3—O—CH_2—CH_3$	8	ether	60
$CH_3—NH—CH_2—CH_3$	37	secondary amine	59
$CH_3CH_2CH_2—NH_2$	48	primary amine	59
$CH_3CH_2CH_2—OH$	97	alcohol	60

Aminas naturales y sintéticas

- Sistemas biológicos: neurotransmisores/ aminoácidos
- Fármacos/ drogas: Fluoxetina / MDMA

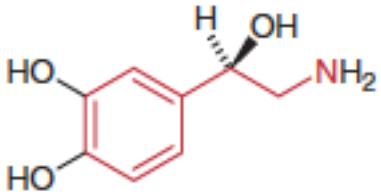


fluoxetine



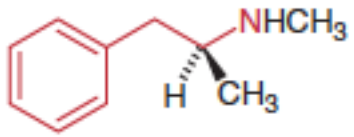
adrenaline
(epinephrine)

a hormone secreted in response to stress
(Chapter 7, introductory molecule)



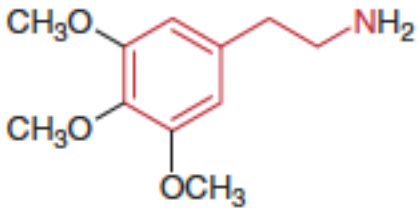
noradrenaline
(norepinephrine)

a neurotransmitter that increases heart rate
and dilates air passages



methamphetamine

an addictive stimulant sold as
speed, meth, or crystal meth



mescaline

a hallucinogen isolated from peyote, a cactus native
to the southwestern United States and Mexico

Aminas naturales y sintéticas

- Sistemas biológicos: neurotransmisores/ aminoácidos
- Fármacos/ drogas: Fluoxetina / MDMA
- Alacaloides: (Figura)

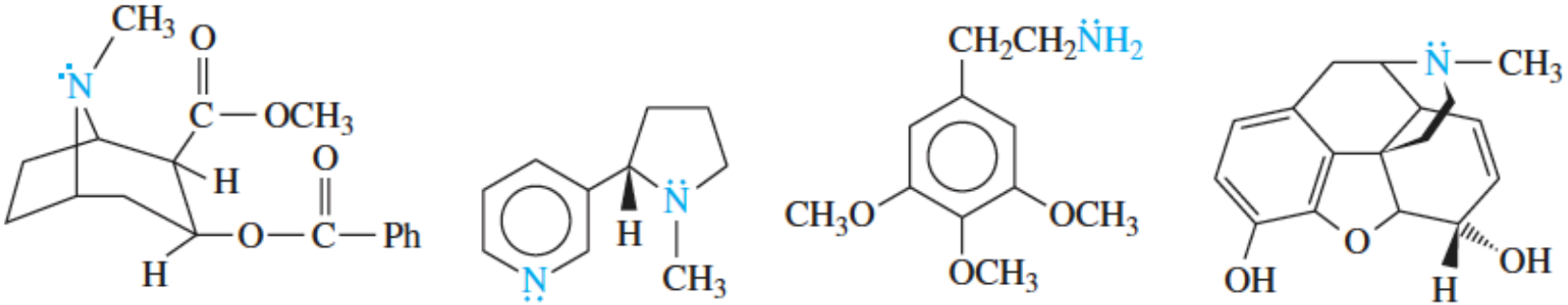
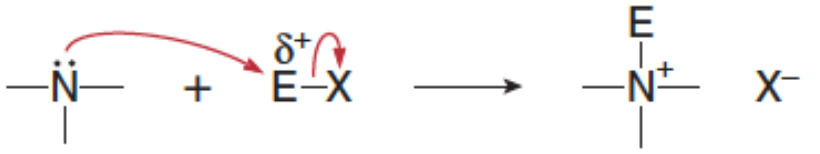


FIGURE 19-2
Some representative alkaloids.

Aminas como bases

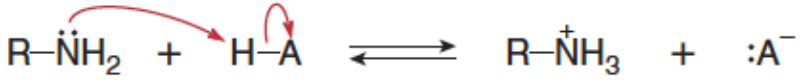
Reaction as a base

Reaction as a nucleophile



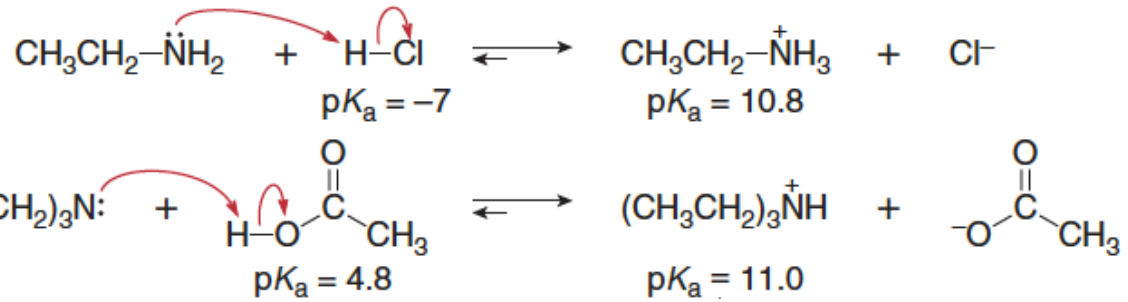
E = an electrophilic site

A Brønsted–Lowry acid–base reaction



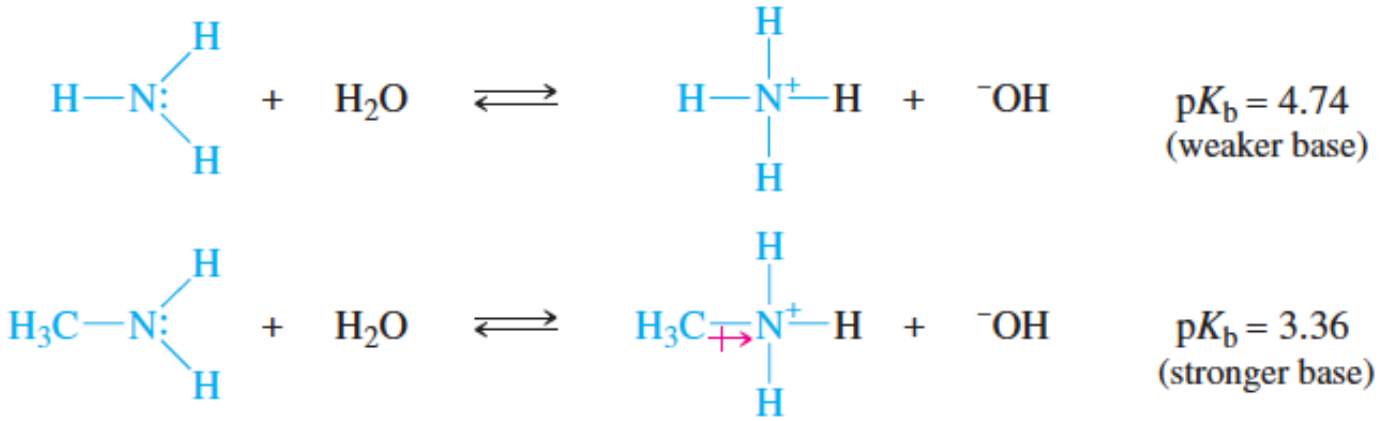
To favor the products, the **pK_a of HA must be < 10.**

Examples



Factores que influyen en la basicidad: sustitución

Aminas 1°, 2° y 3° son más básicas que NH_3

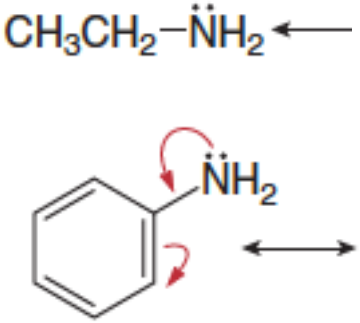


		pK_b	
dimethylamine	5.3×10^{-4}	3.28	10.72
trimethylamine	5.5×10^{-5}	4.26	9.74

Efectos estéricos y estabilización de productos influyen en la basicidad de aminas sustituidas

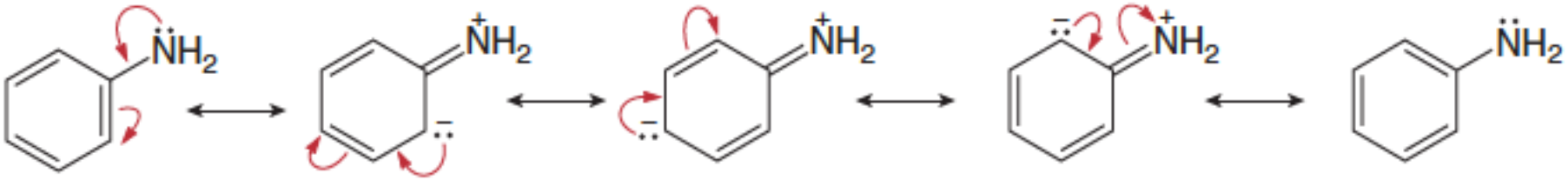
Factores que influyen en la basicidad: resonancia

Qué tan disponibles están los pares de electrones no enlazados?

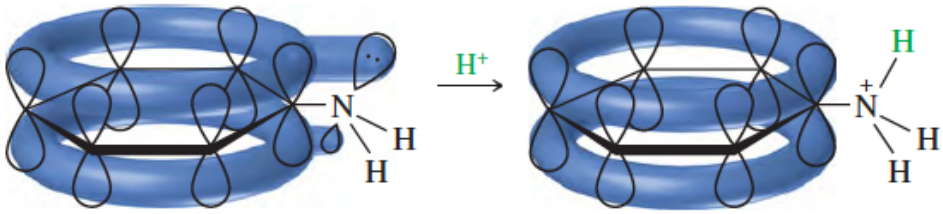


Factores que influyen en la basicidad: resonancia

$CH_3CH_2-\ddot{N}H_2$ ← **The electron pair is localized on the N atom.**

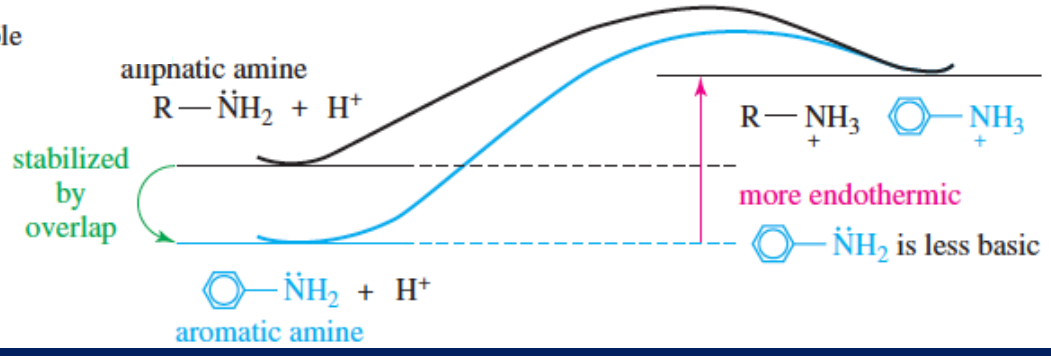


The electron pair is delocalized on the benzene ring.



aniline
stabilized by overlap with the ring

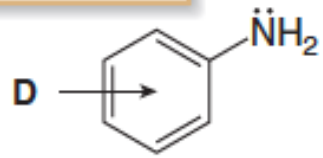
anilinium ion
no overlap is possible



Factores que influyen en la basicidad: resonancia

Grupos electro-donores aumentan la basicidad de los derivados de anilina

D = electron-donor group

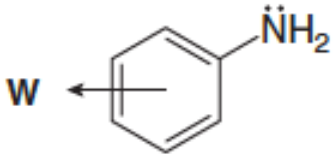


D makes the amine more basic than aniline.

D
$-NH_2$
$-OH$
$-OR$
$-NHCOR$
$-R$

Grupos electro-atractores disminuyen la basicidad de los derivados de anilina

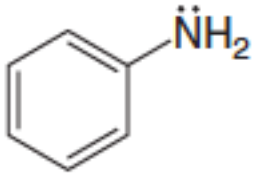
W = electron-withdrawing group



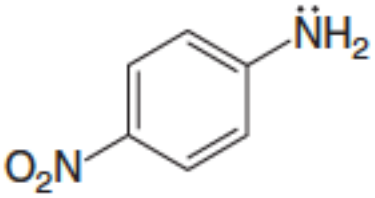
W makes the amine less basic than aniline.

W	
$-X$	$-CN$
$-CHO$	$-SO_3H$
$-COR$	$-NO_2$
$-COOR$	$-NR_3^+$
$-COOH$	

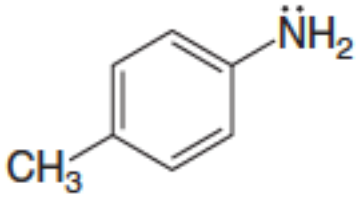
Ejercicio: orden creciente de basicidad



aniline



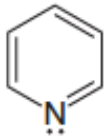
p-nitroaniline



p-methylaniline
(*p*-toluidine)

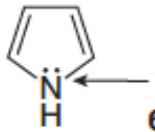
Factores que influyen en la basicidad: resonancia

Pyridine



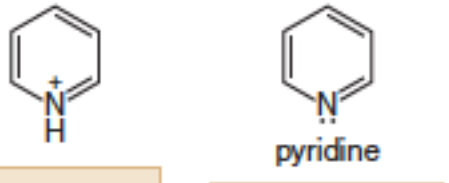
The lone pair resides in an sp^2 hybrid orbital.

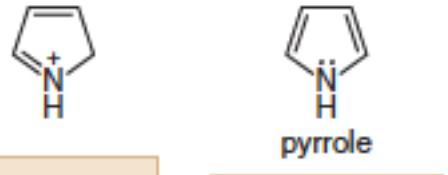
Pyrrole



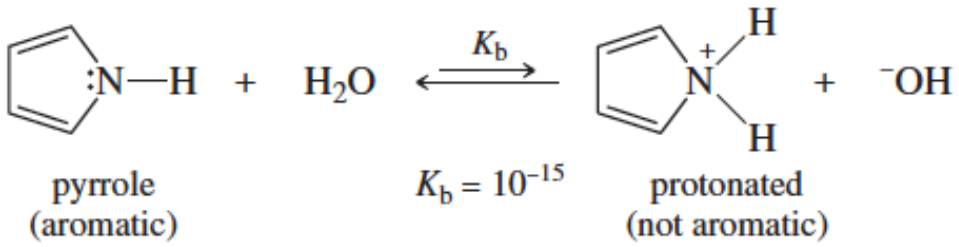
These 2 electrons are part of the 6 π electrons of the aromatic ring.

The lone pair resides in a *p* orbital and is delocalized in the ring.



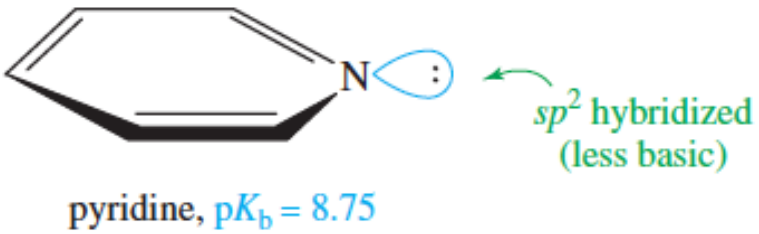


- **Pyrrole is much less basic than pyridine because its lone pair of electrons is part of the aromatic π system.**

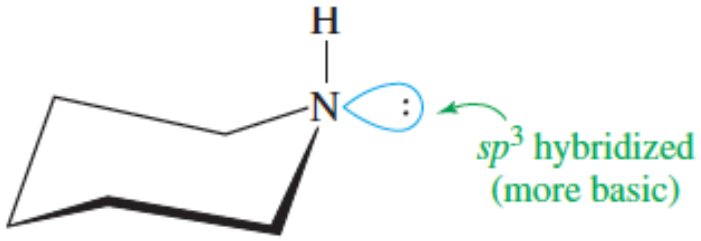


Factores que influyen en la basicidad: hibridación

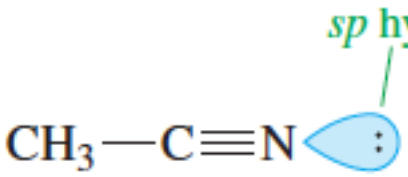
A mayor carácter S menos básica es la amina



pyridine, $pK_b = 8.75$



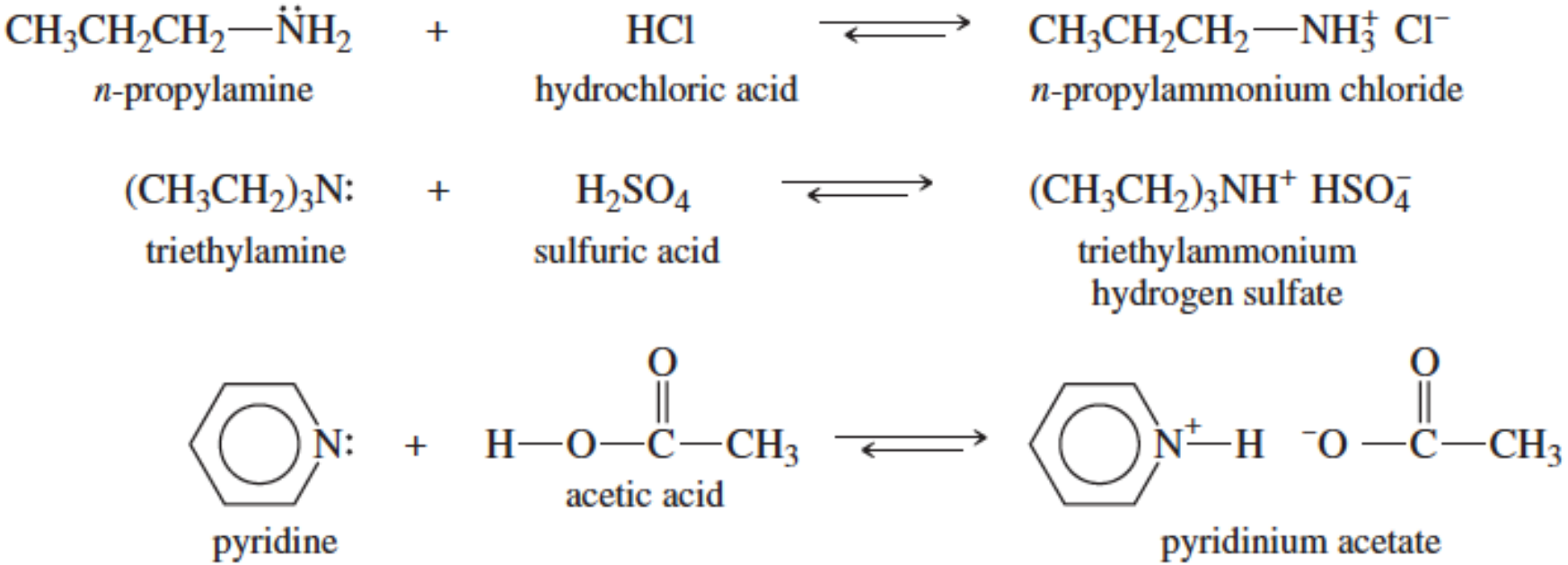
piperidine, $pK_b = 2.88$



very weakly basic

$pK_b = 24$

Formación de sales

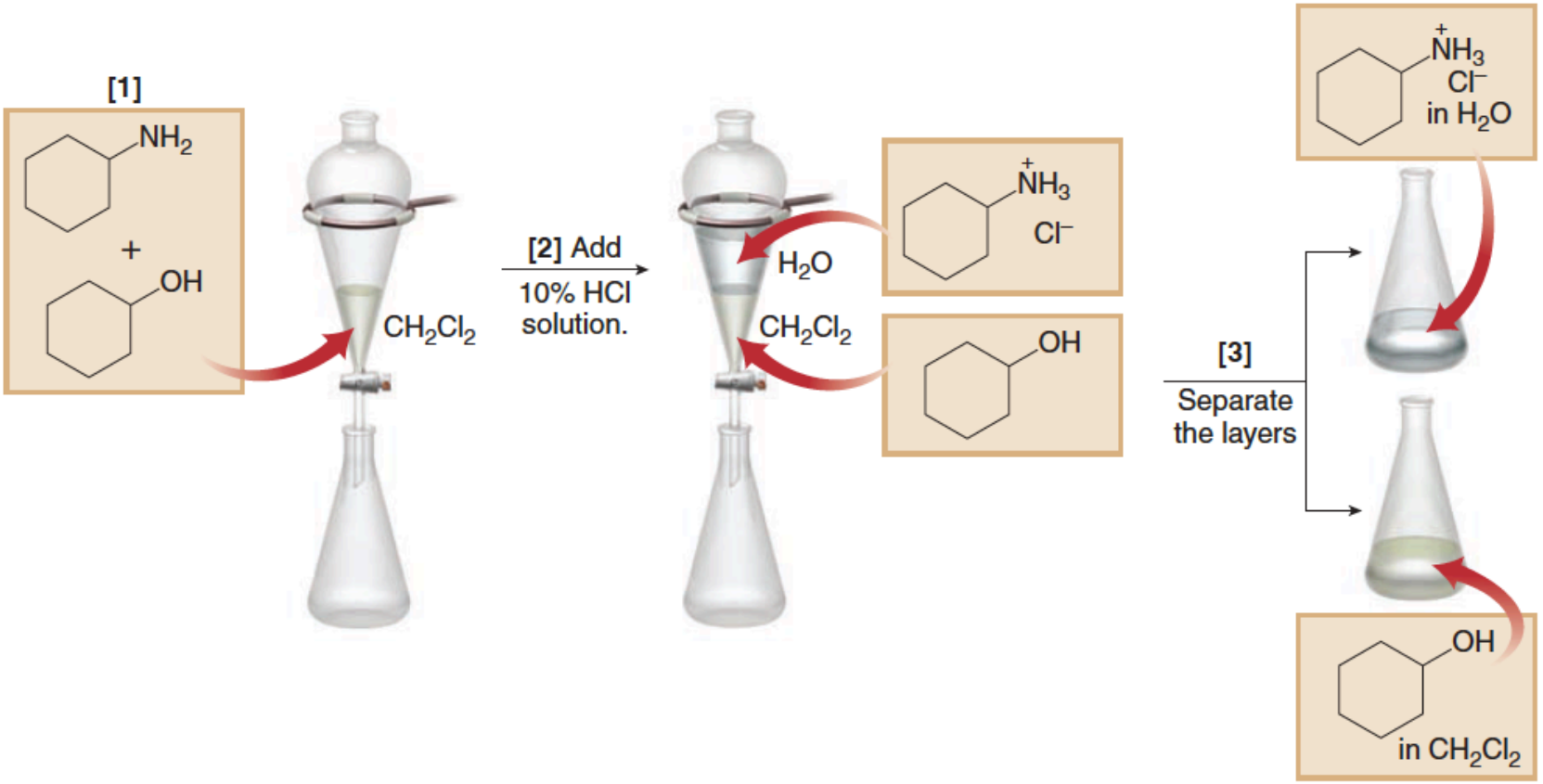


Extracción - separación

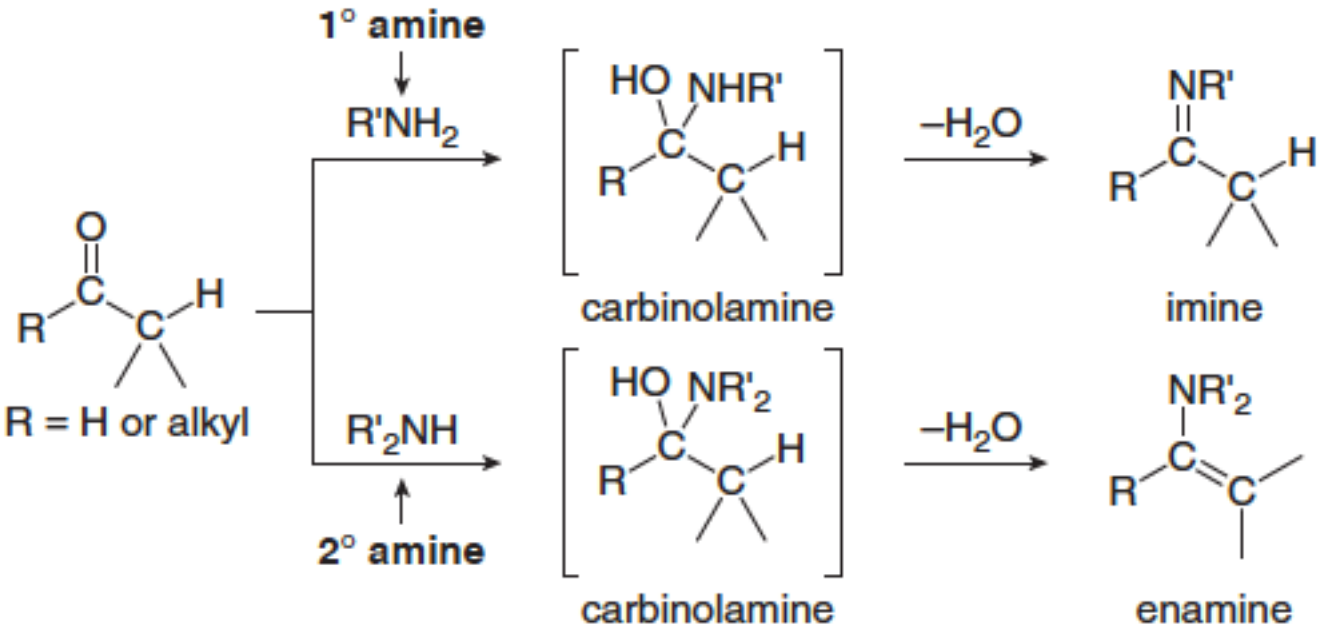
Step [1] Dissolve cyclohexylamine and cyclohexanol in CH_2Cl_2.

Step [2] Add 10% HCl solution to form two layers.

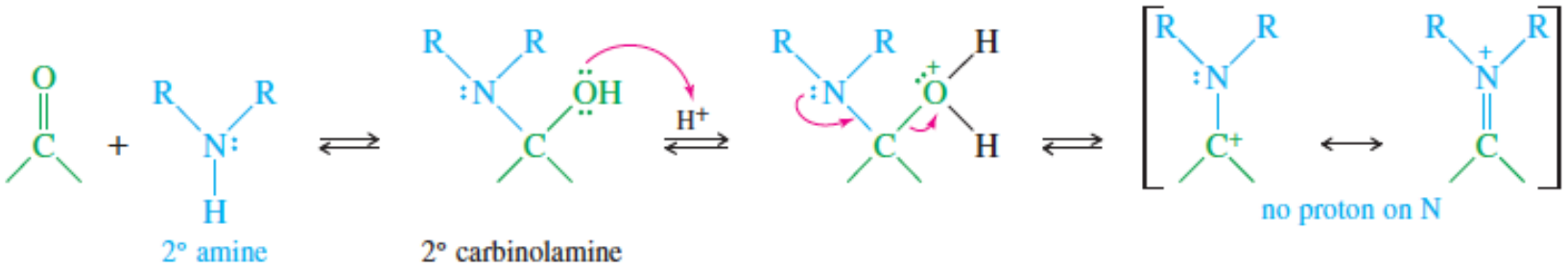
Step [3] Separate the layers.

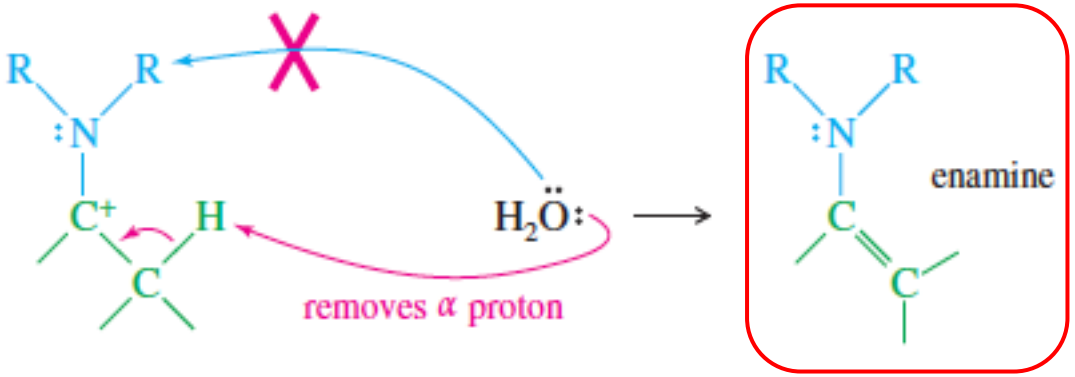


Reactividad: amina con aldehídos y cetonas

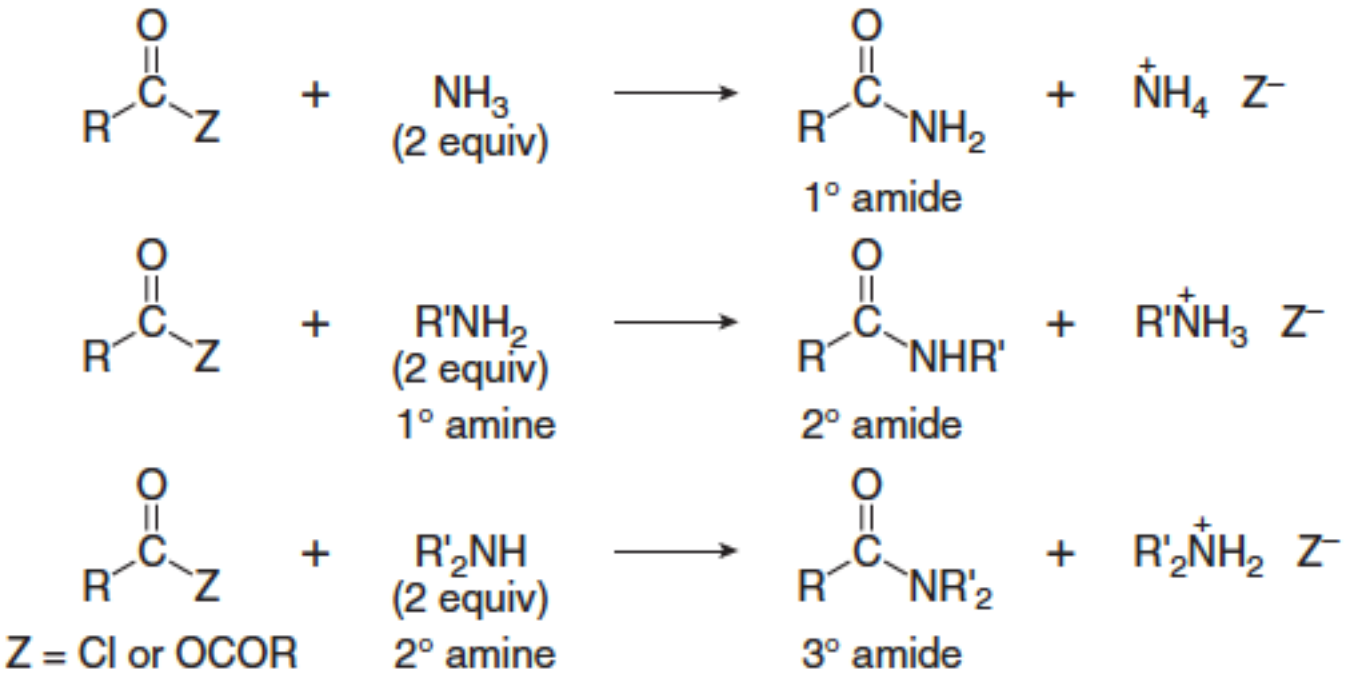


Reactividad: 1- enaminas



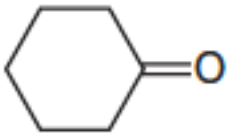


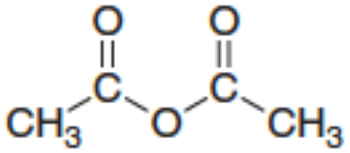
Reactividad: aminas con cloruros de ácido o anhídridos

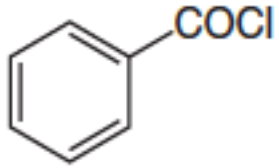


ejercicios

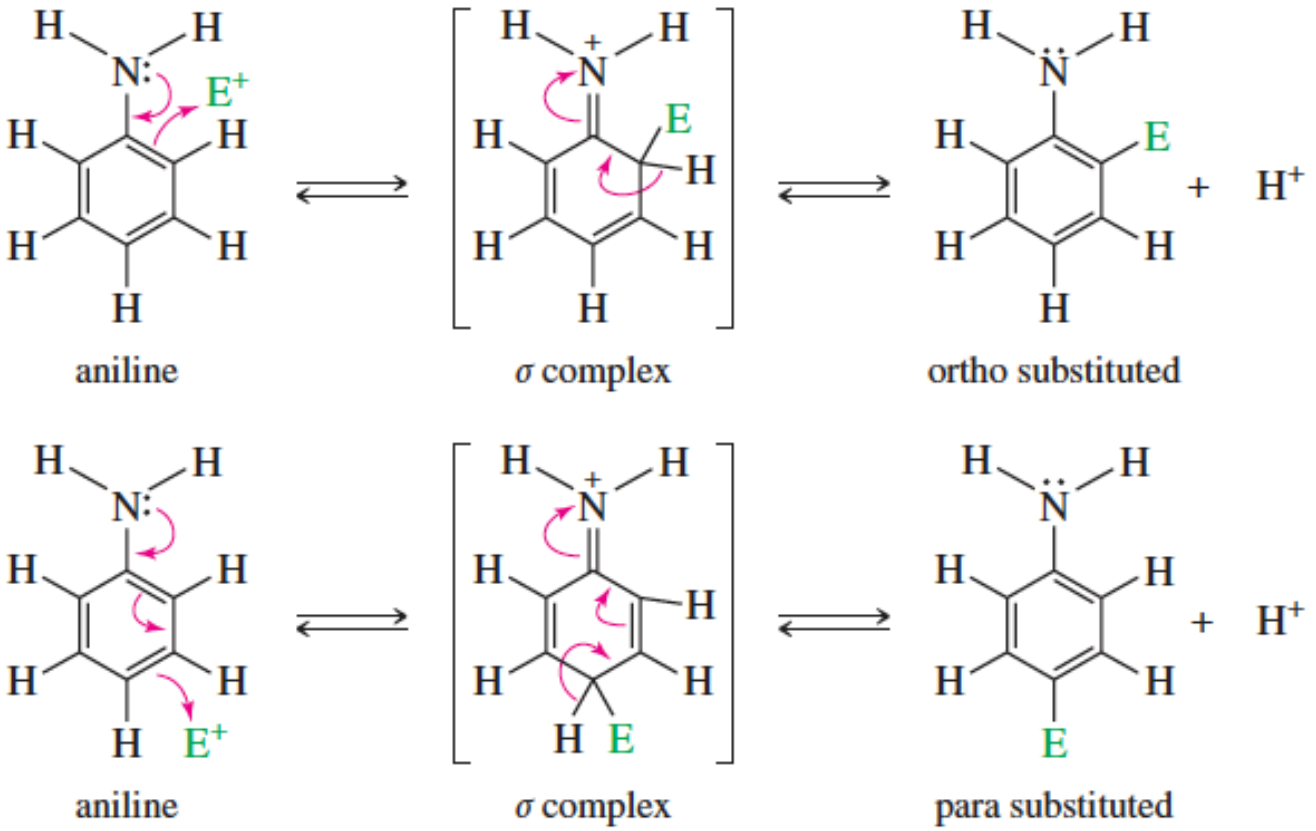
[1] $CH_3CH_2CH_2NH_2$; [2] $(CH_3CH_2)_2NH$.

a. 

b. 

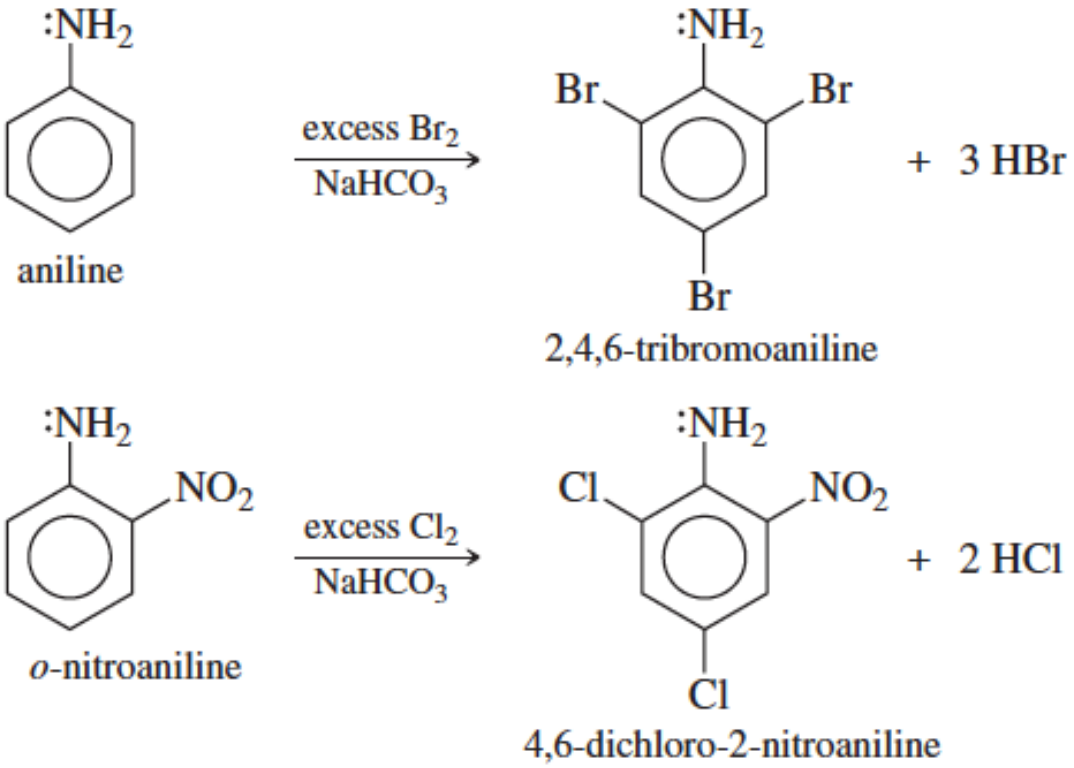
c. 

Sustitución electrofílica arómatica de arilaminas



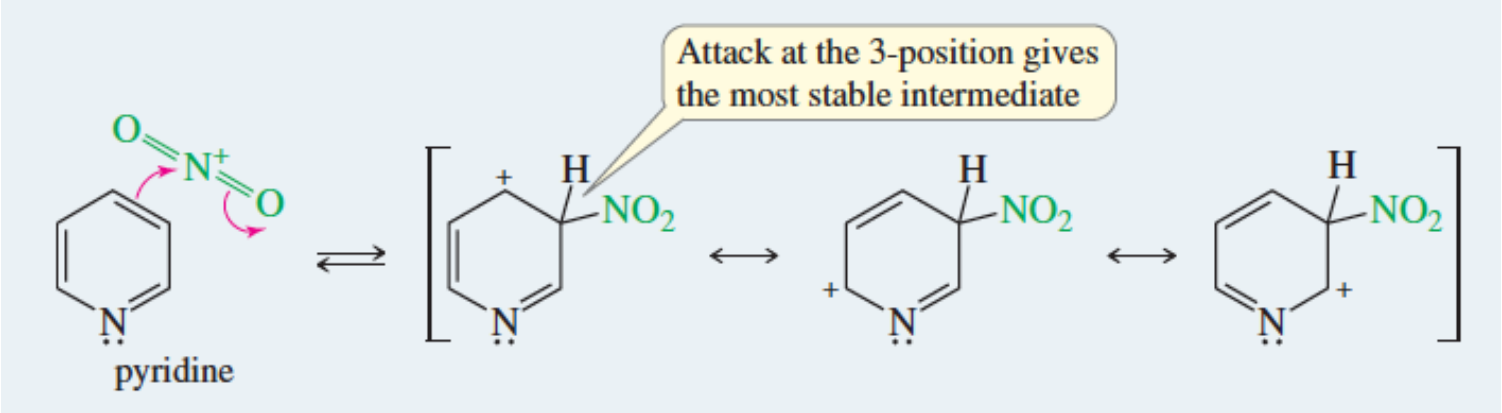
- Promueve ataque en posición orto o para estabilizando complejo sigma.
- Son directores orto y para.
- Al reaccionar con reactivos muy ácidos pueden protonar el grupo amino, el cual es un desactivador fuerte.

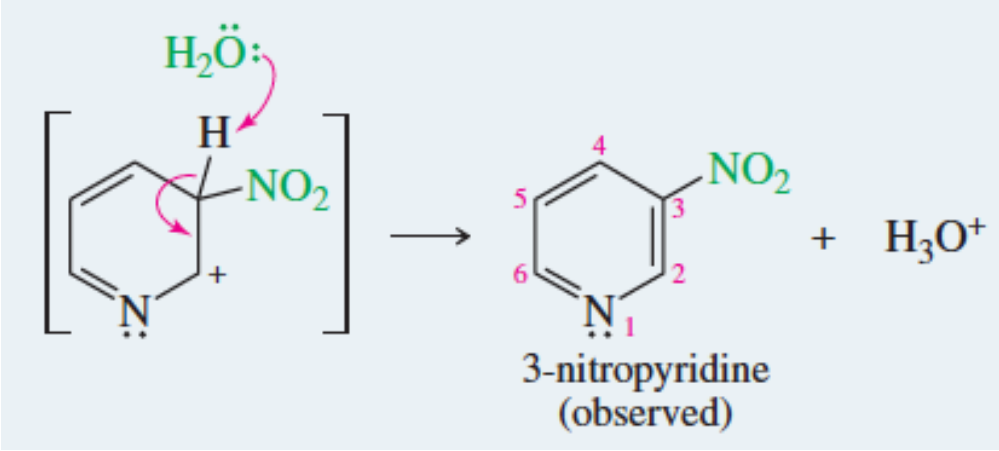
Sustitución electrofílica arómatica de arilaminas



Sustitución electrofílica arómatica de piridina

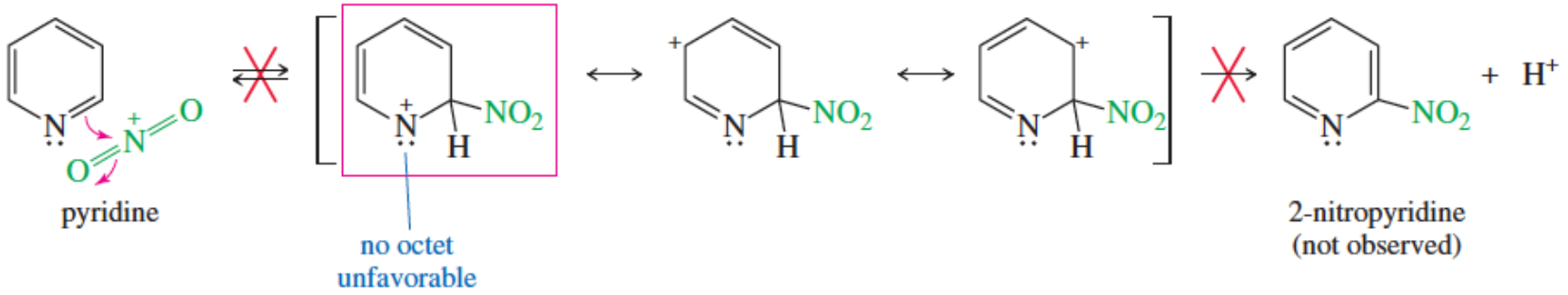
Mecanismo

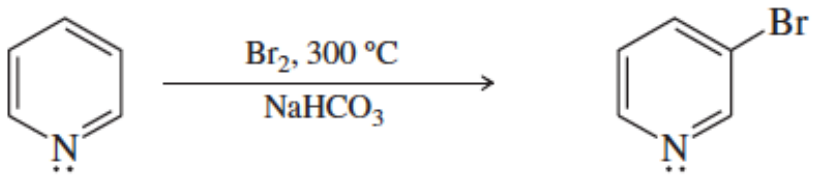


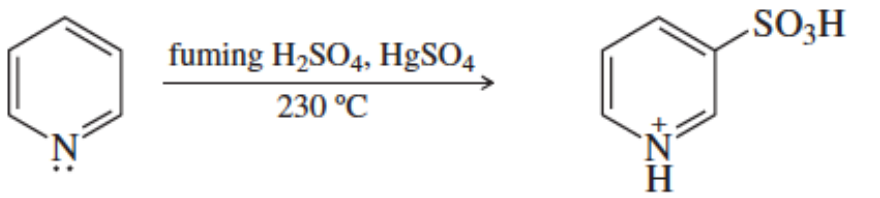


Sustitución electrofílica arómatica de piridina

Attack at the 2-position (or 4-position) is not observed.

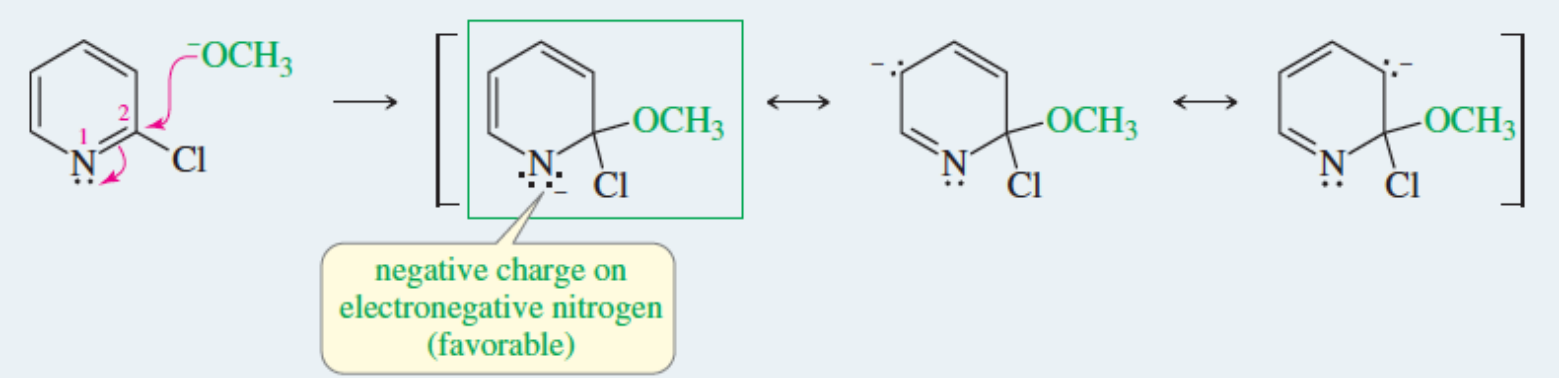


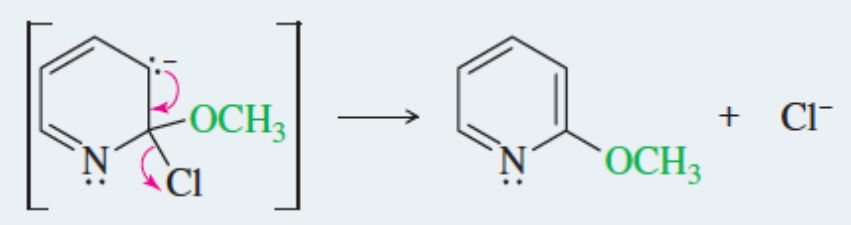




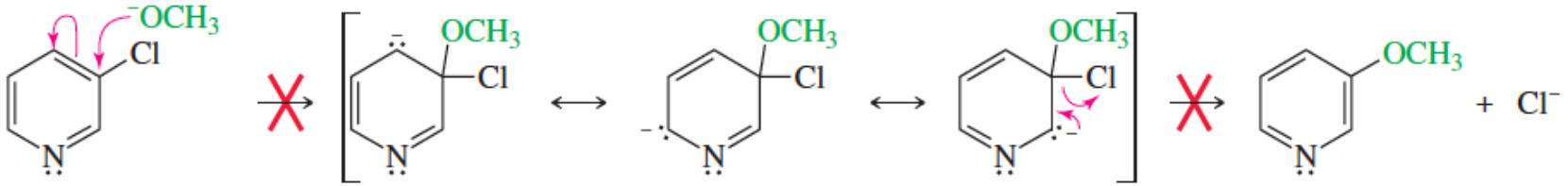
Sustitución nucleofílica arómatica de piridina

Mecanismo



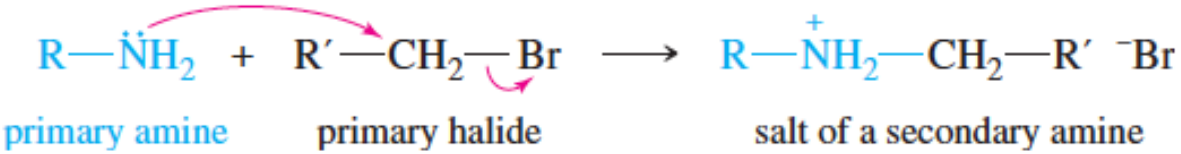


Nucleophilic attack at the 3-position (not observed)

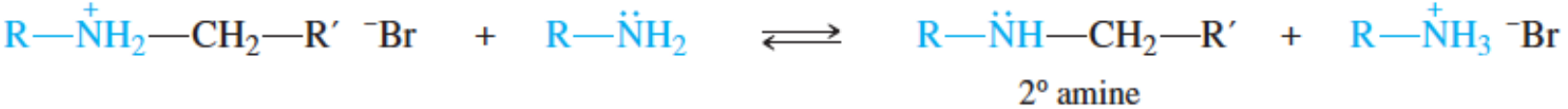


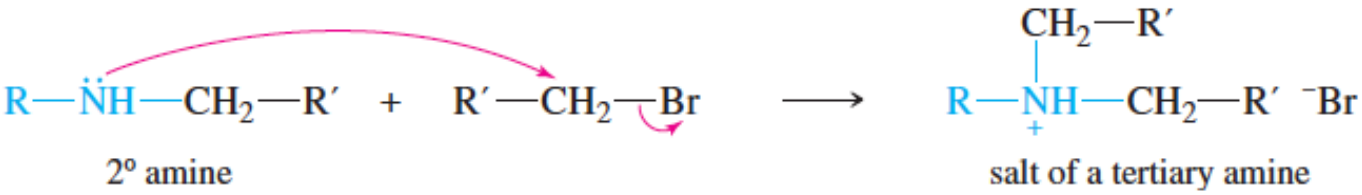
(no delocalization of negative charge onto N)

Alquilación de aminas por halogenuros de alquilo (R-X)



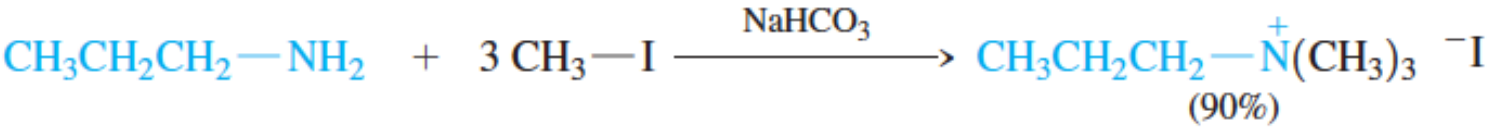
Vía SN2 (R-X 1°
R-X 2° bajos %)



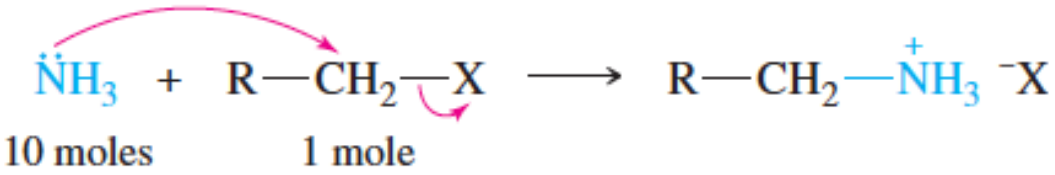


Alquilación de aminas por halogenuros de alquilo (R-X)

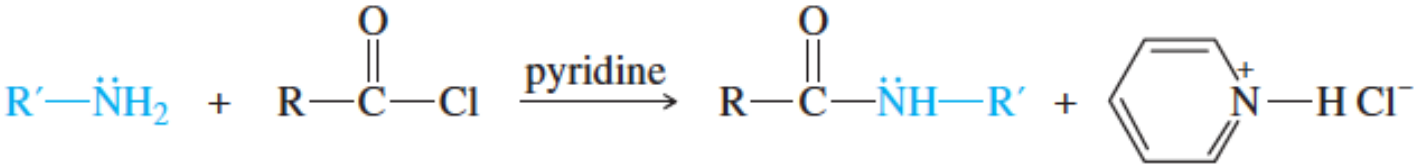
Alquilación exhaustiva



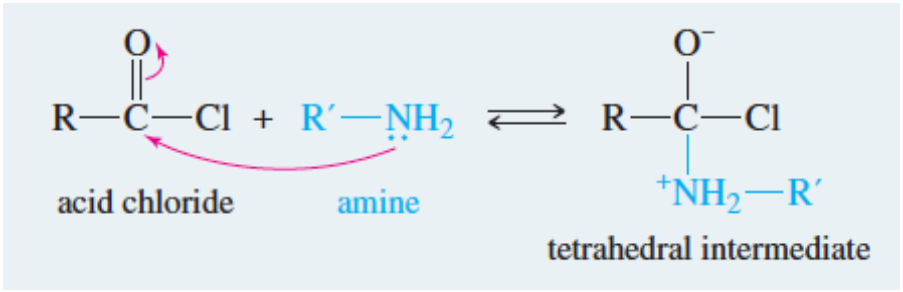
Exceso amoniaco

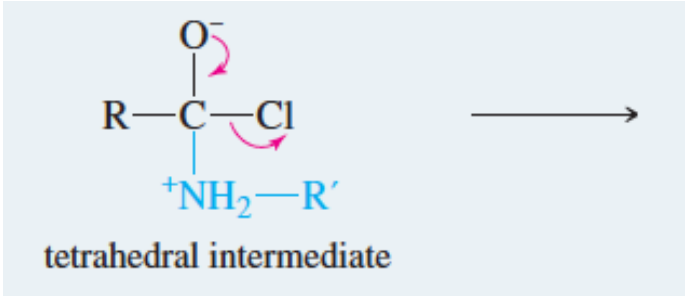


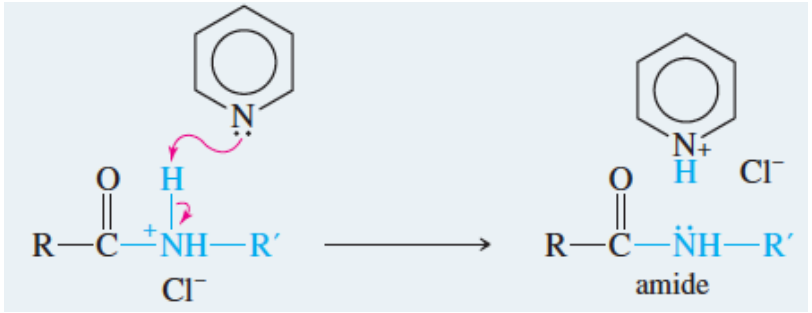
Acilación de aminas por cloruros de ácido



mecanismo

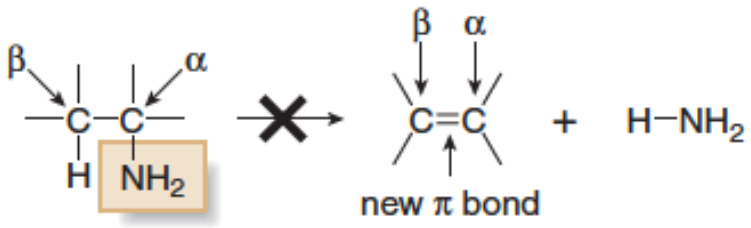






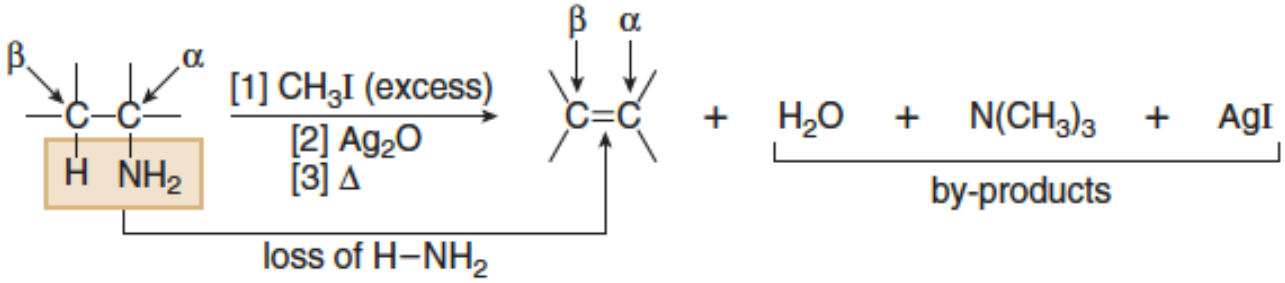
Eliminación de Hofmann

Amines and β elimination

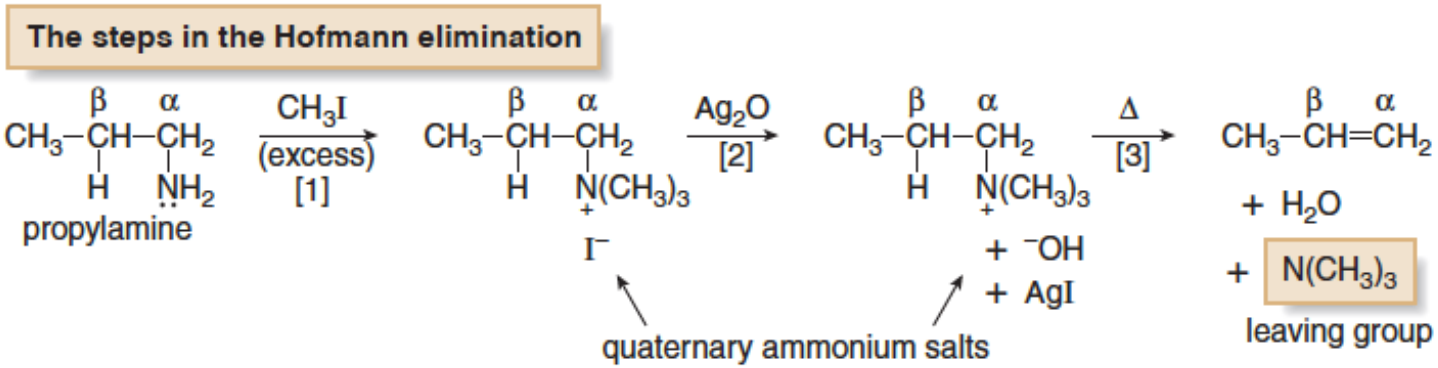


Problem: $^{-}NH_2$ is a poor leaving group.

Hofmann elimination



Eliminación de Hofmann

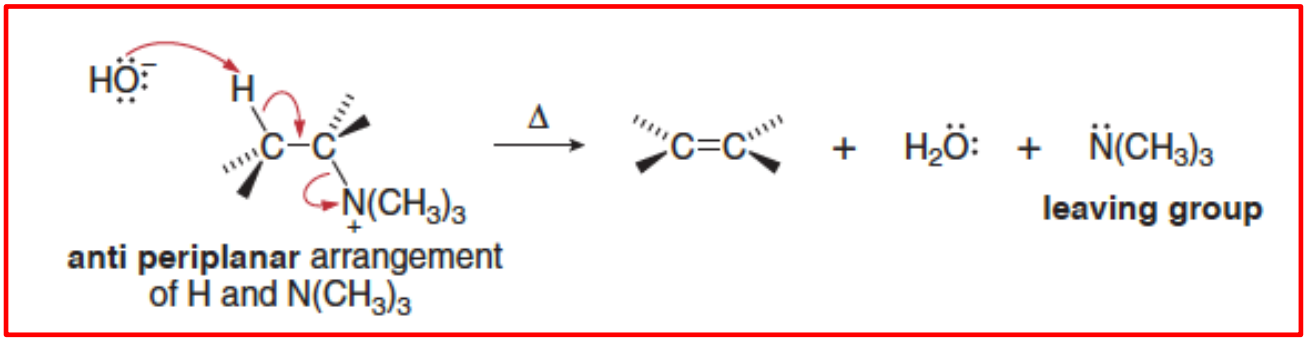


SN2

Cambio de anión

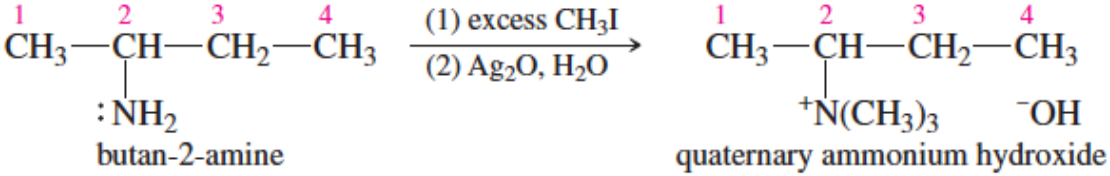
E2 base fuerte
Nuevo enlace pi

mecanismo

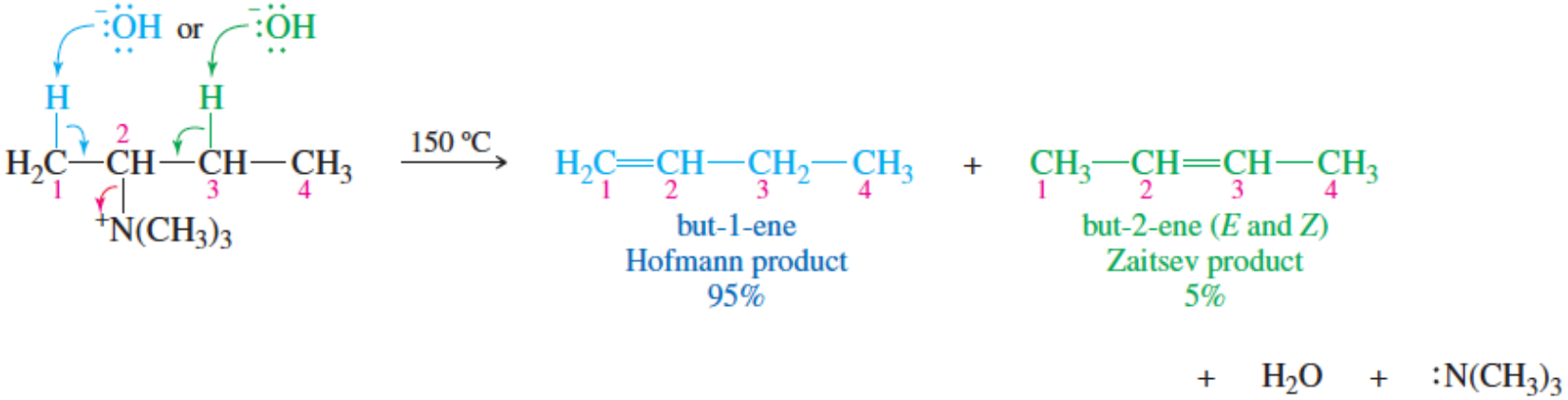


Eliminación de Hofmann

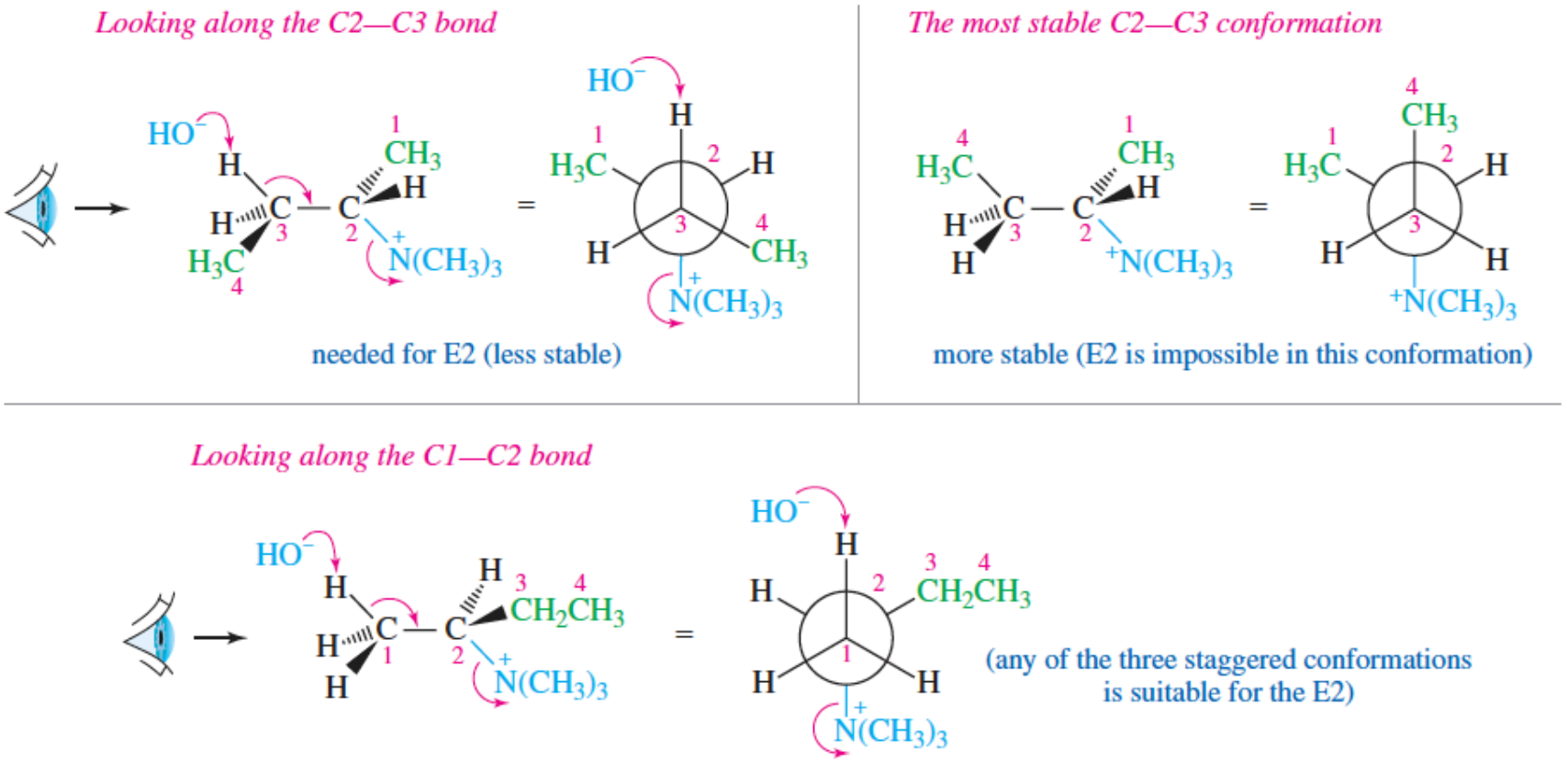
Exhaustive methylation and conversion to the hydroxide salt



Heating and Hofmann elimination



Eliminación de Hofmann



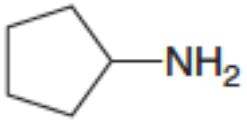
- Volumen grupo saliente (arreglo-coplanar)
- Estado de transición estable o más probable

Eliminación de Hofmann

Dibuje el producto al tratar los siguientes compuestos con :
1) CH_3I en exceso, 2) Ag_2O, 3) calor (Δ)

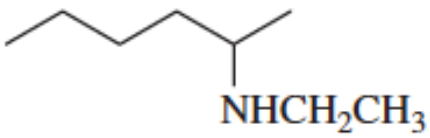
a. $CH_3CH_2CH_2CH_2{-}NH_2$

b. $(CH_3)_2CHNH_2$

c. 

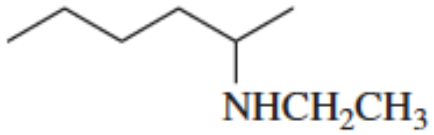
Eliminación de Hofmann

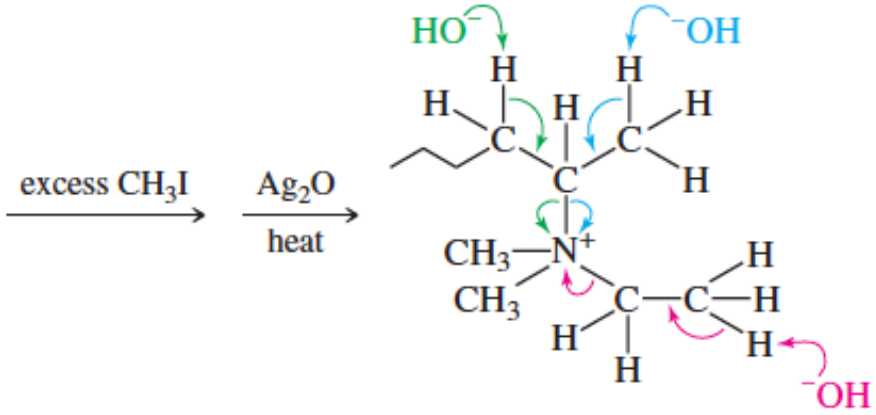
Predict the major product(s) formed when the following amine is treated with excess iodomethane, followed by heating with silver oxide.

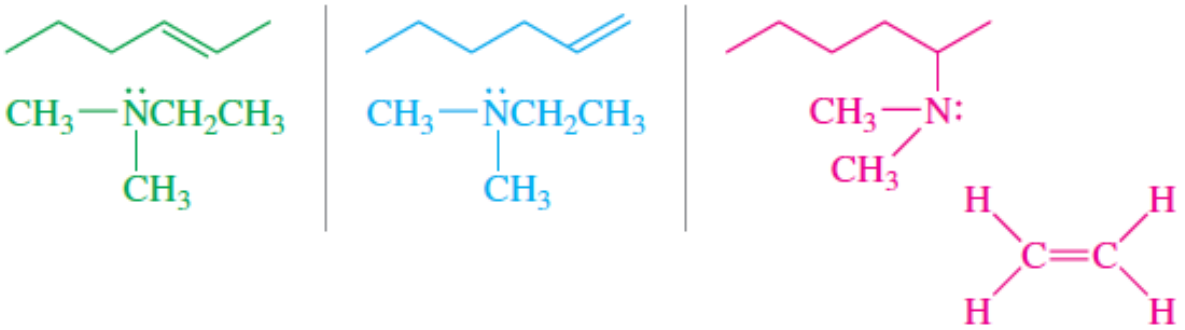


Eliminación de Hofmann

Predict the major product(s) formed when the following amine is treated with excess iodomethane, followed by heating with silver oxide.





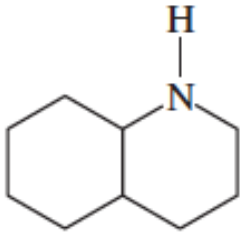


Eliminación de Hofmann

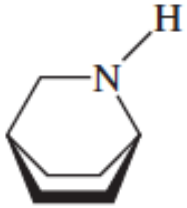
Predict the major products formed when the following amines undergo exhaustive methylation, treatment with Ag_2O, and heating.

(a) hexan-2-amine **(b)** 2-methylpiperidine **(c)** *N*-ethylpiperidine

(d)

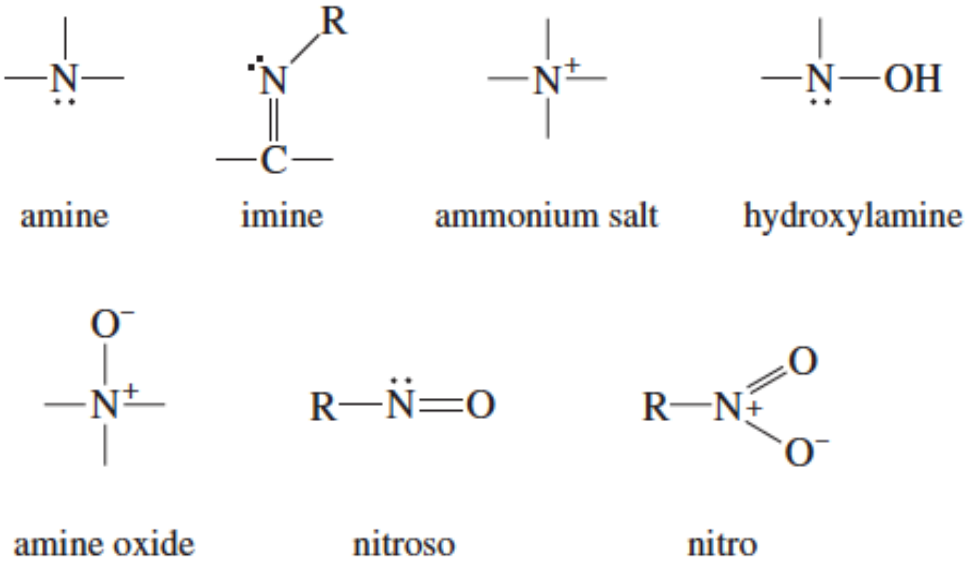


(e)

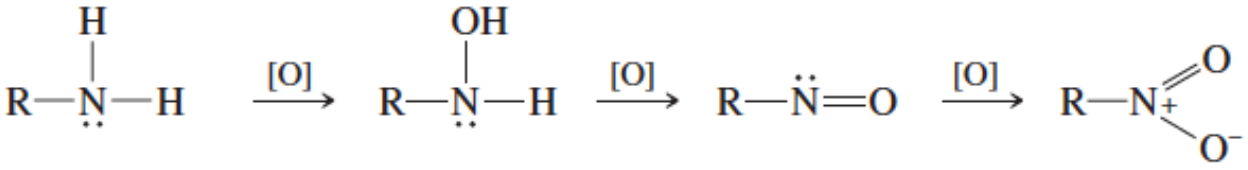


(f)

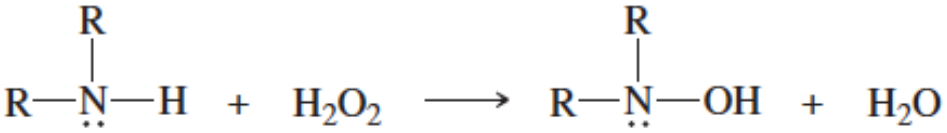
Oxidación de aminas



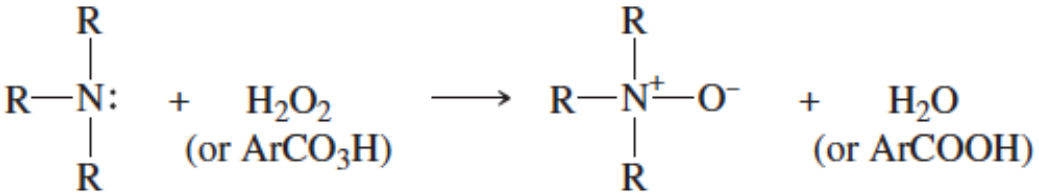
Oxidación de aminas - Eliminación de Cope reactivo



1° amine hydroxylamine nitroso nitro



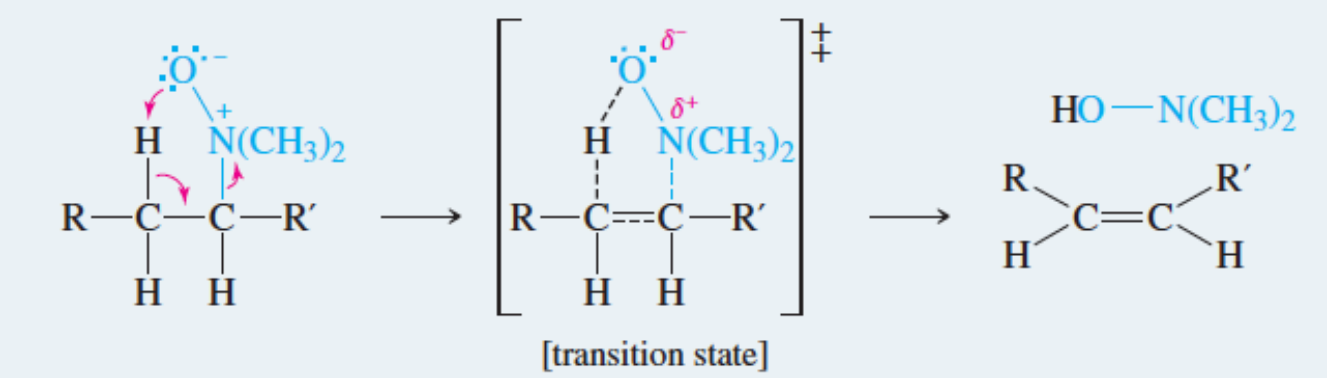
2° amine a 2° hydroxylamine



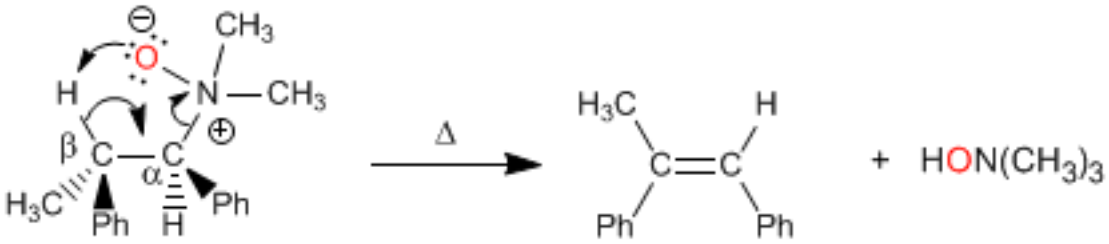
3° amine 3° amine oxide

Eliminación de Cope

Mecanismo

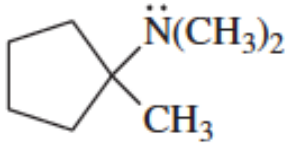


Eliminación sin (estereoquímica)

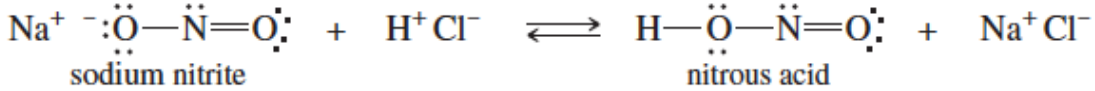


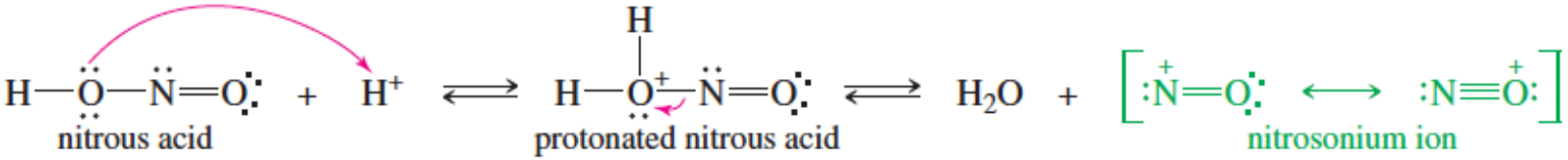
Eliminación de Cope

Predict the products expected when the following compound is treated with H_2O_2 and heated.

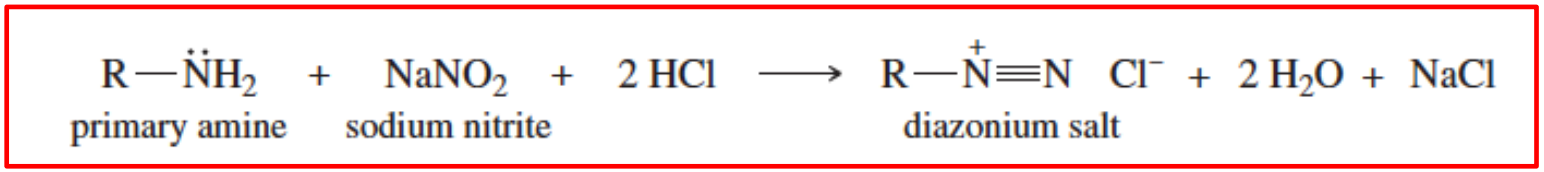


Reacciones con ácido nitroso



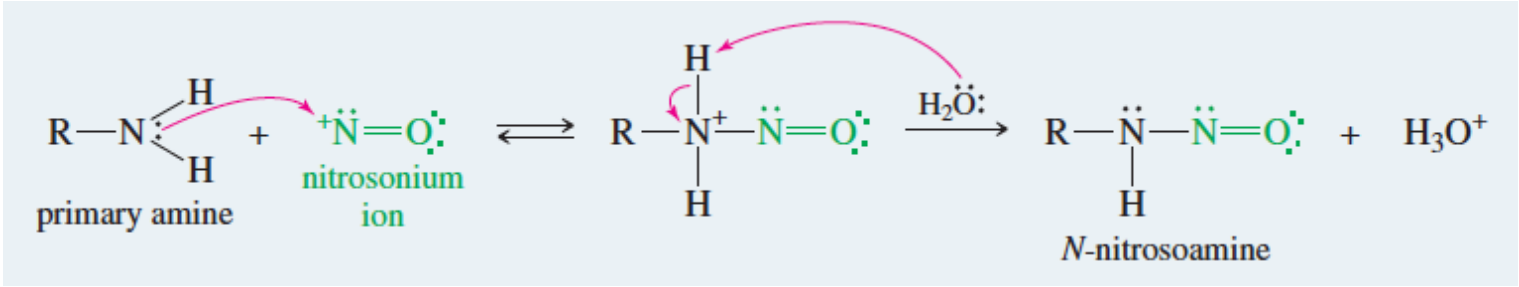


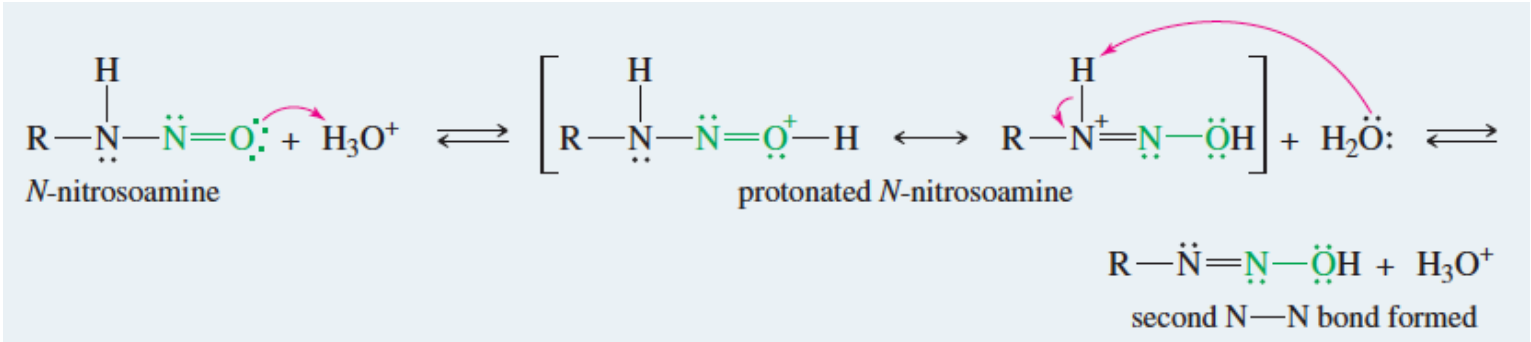
Electrófilo fuerte

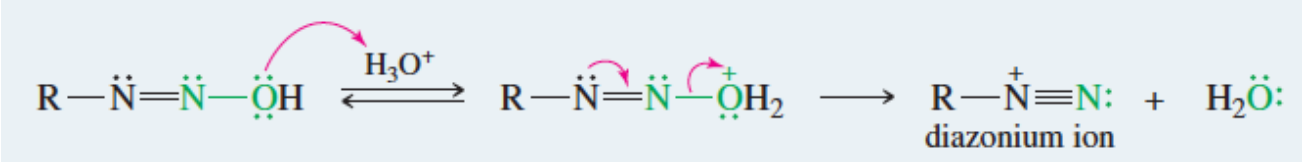


Formación de sales de diazonio

Mecanismo: aminas primarias



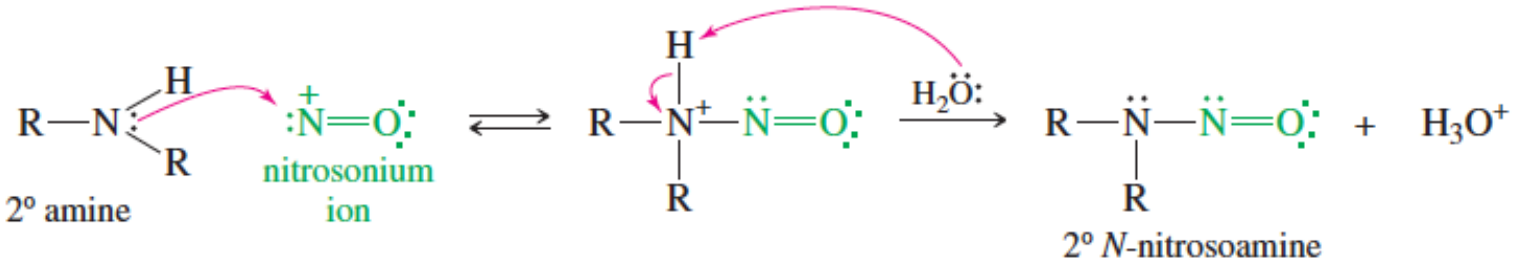




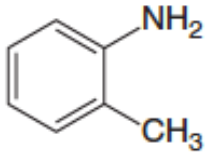
Alquilaminas inestables
Arilaminas estables

Formación de N-nitrosoamina

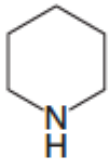
Mecanismo: aminas secundarias

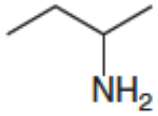


Draw the product formed when each compound is treated with $NaNO_2$ and HCl.

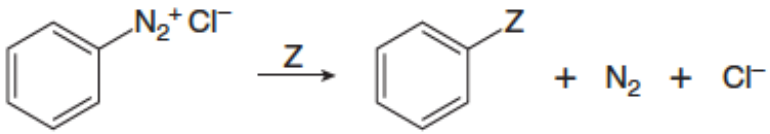
a. 

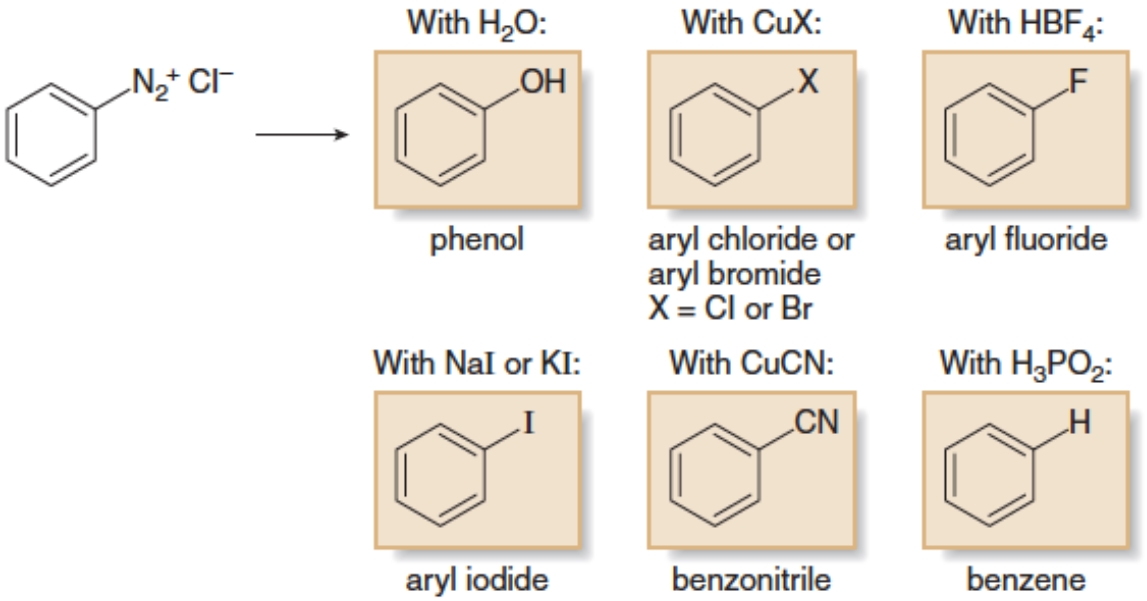
b. $CH_3CH_2-\underset{\underset{H}{|}}{N}-CH_3$

c. 

d. 

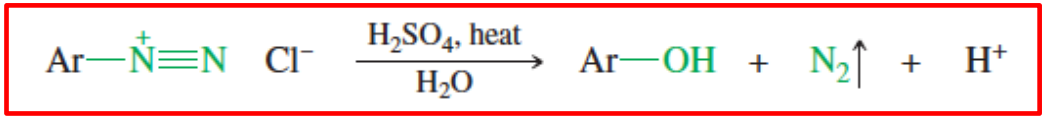
Sales de arildiazonio como intermediaros de síntesis

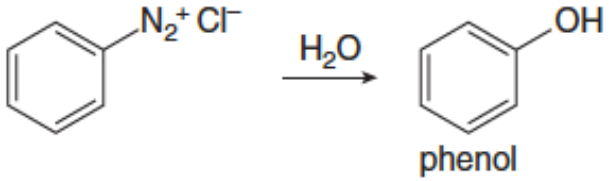




Sales de arildiazonio como intermediaros de síntesis

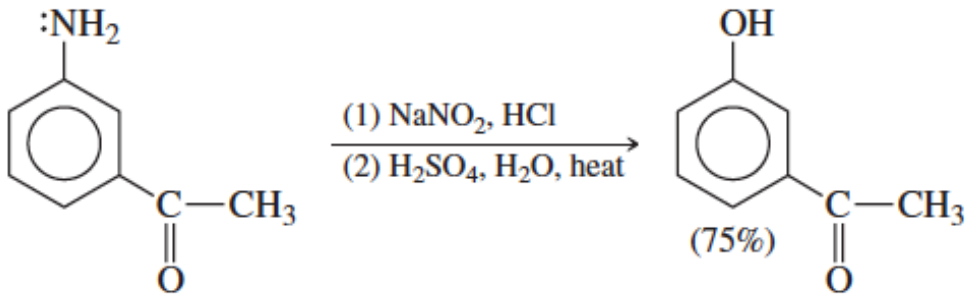
Síntesis de fenoles





No requiere:

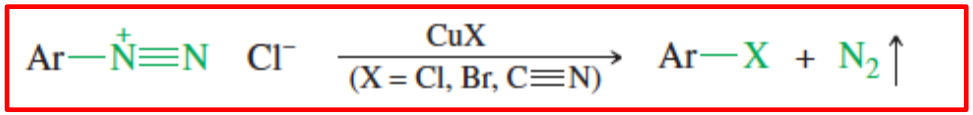
- Sustituyentes atractores (como en las Rxs de SNAr)
- Bases o Nu fuertes

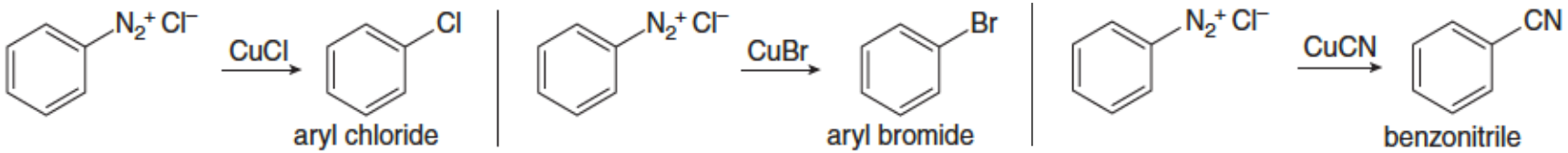


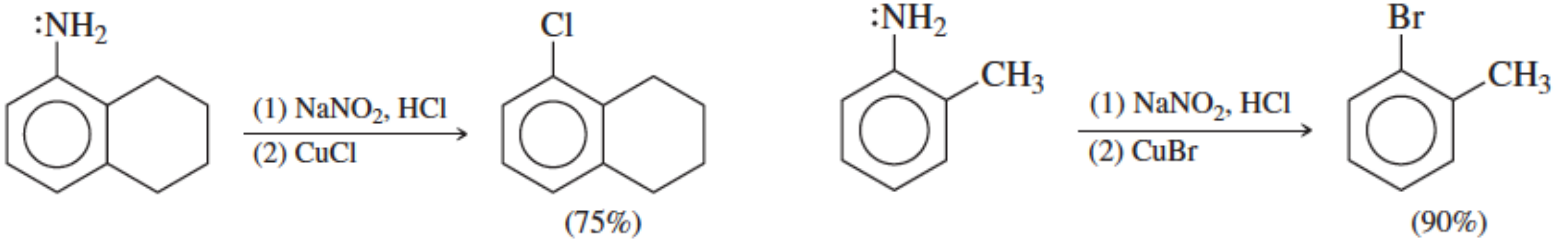
Sales de arildiazonio como intermediaros de síntesis

Síntesis de halogenuros de arilo

Reacción de Sandmeyer



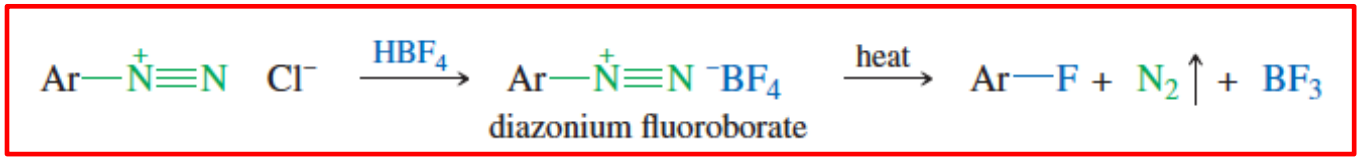




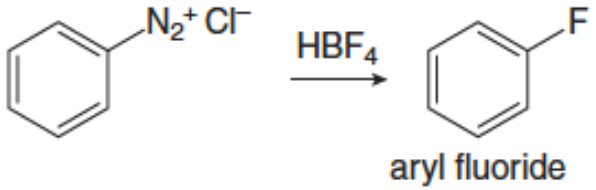
Halogenación directa

Sales de arildiazonio como intermediaros de síntesis

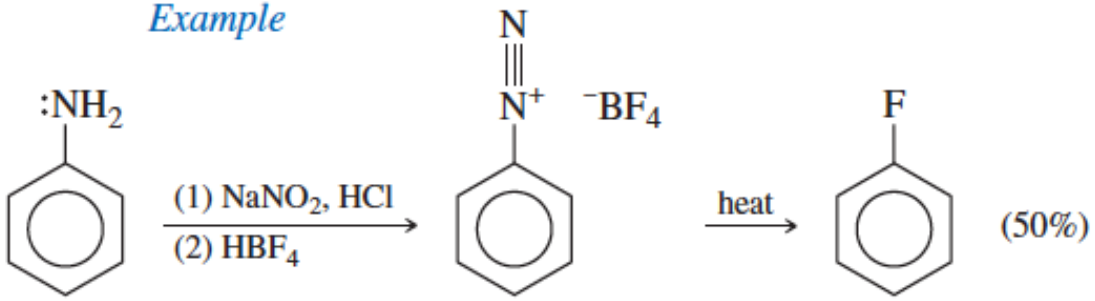
Síntesis de fluoruro de arilo



Ácido fluoroborato (HBF_4)

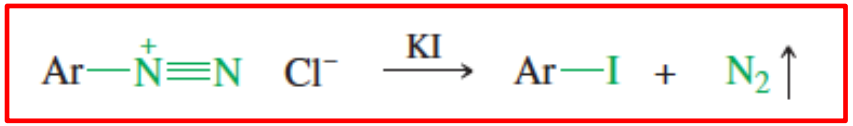


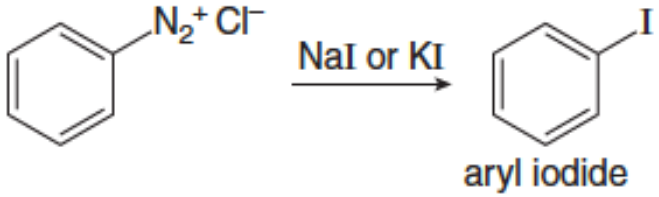
Example



Sales de arildiazonio como intermediaros de síntesis

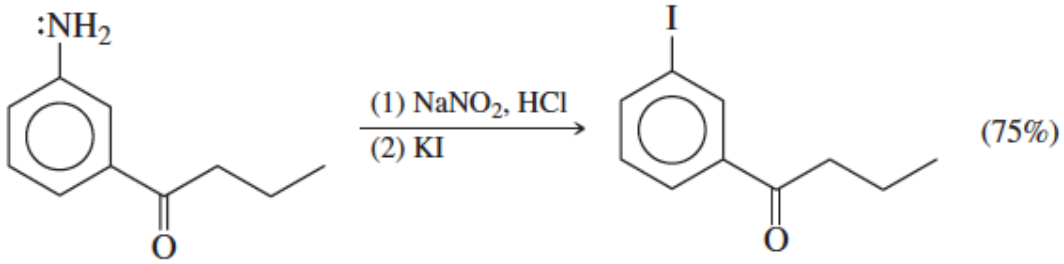
Síntesis de yoduro de arilo





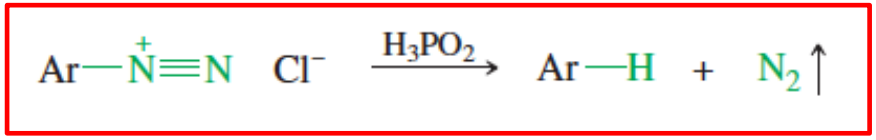
Mejor alternativa que utilizar I_2 y ácidos de Lewis (Yodinación)

Example

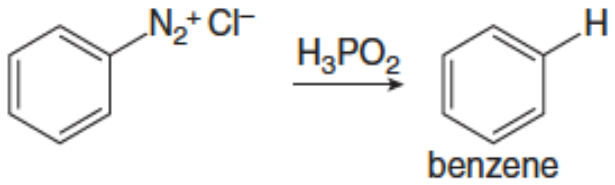


Sales de arildiazonio como intermediaros de síntesis

Sustitución del grupo diazonio por hidrógenos: desaminación de anilinas

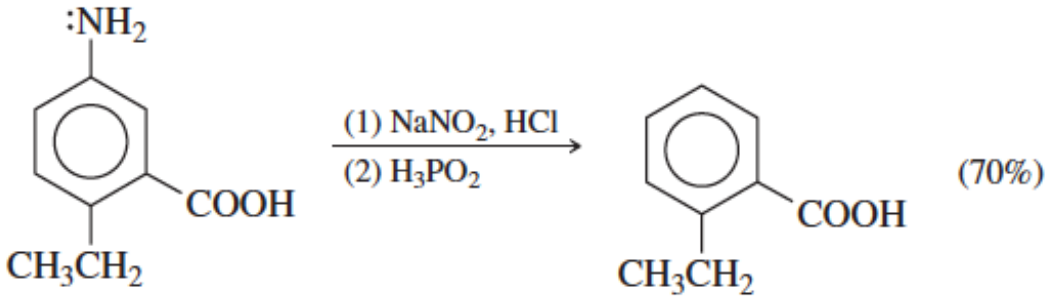


Ácido hipofosforoso (H_3PO_2)

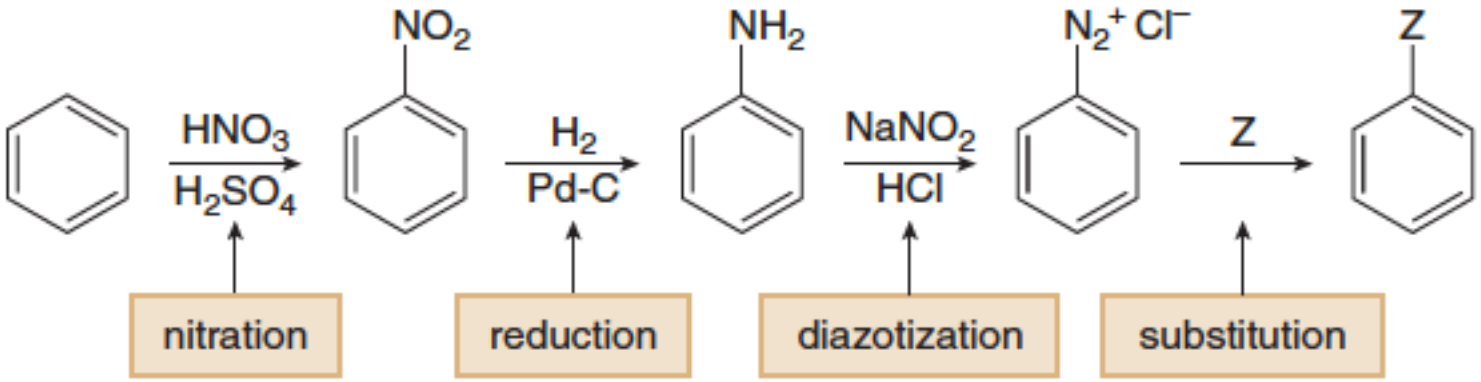


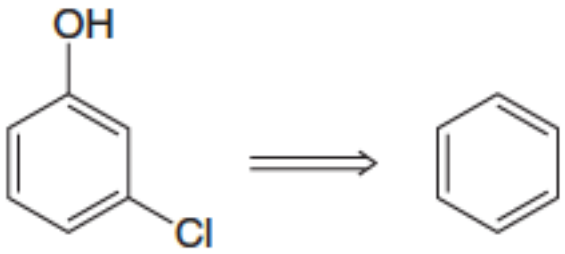
Patrones de sustitución / reduce funcionalización del anillo de benceno

Example



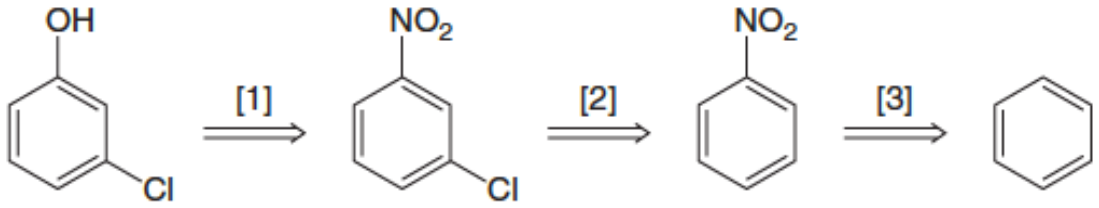
Sales de diazonio en síntesis orgánica




OH
Cl

solución

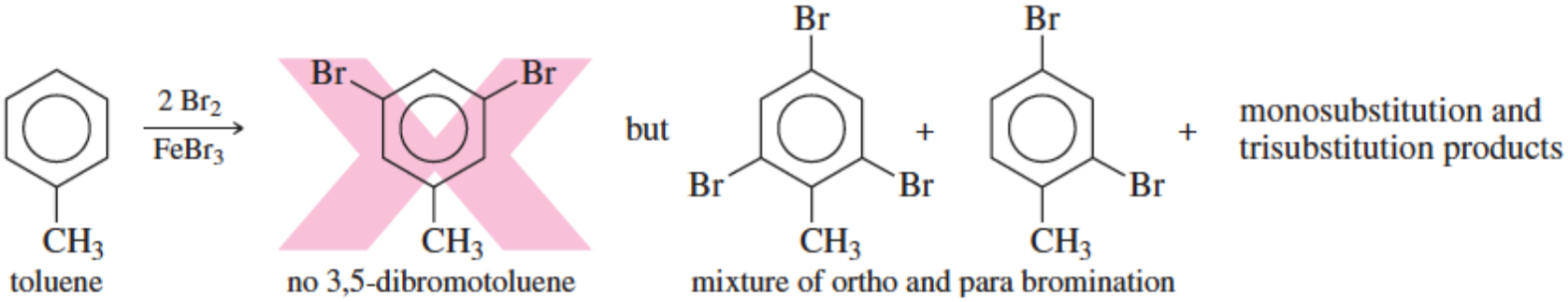
OH y Cl son directores o y p, pero se encuentran en m. El OH debe ser formado por medio de una sal de diazonio

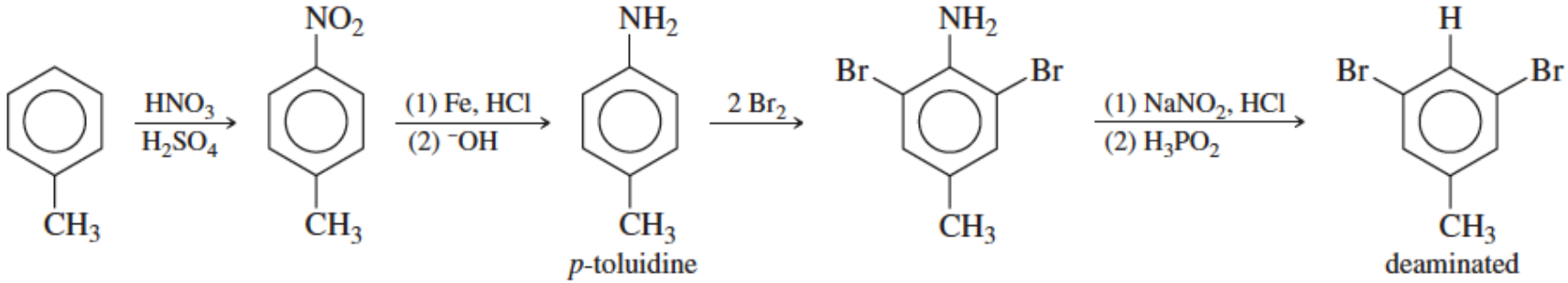


ejercicios

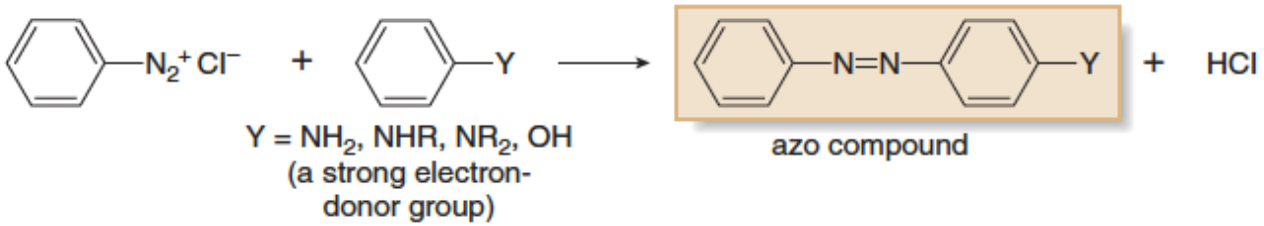
Show how you would convert toluene to 3,5-dibromotoluene in good yield.

ejercicios

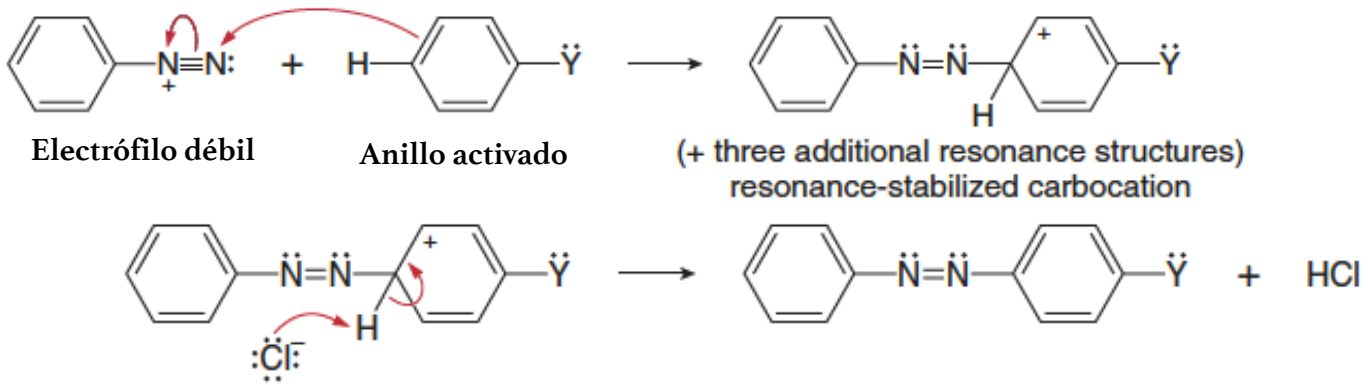

2 Br2
FeBr3
Br
Br
CH3
toluene
CH3
no 3,5-dibromotoluene
but
Br
Br
Br
+
Br
Br
Br
CH3
CH3
CH3
+
monosubstitution and
trisubstitution products
mixture of ortho and para bromination

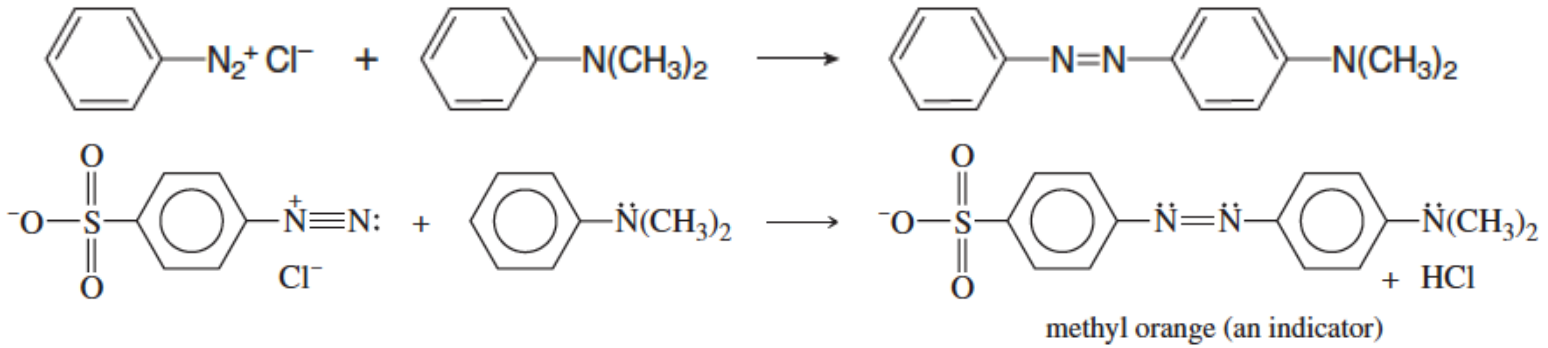

CH3
HNO3
H2SO4
NO2
CH3
(1) Fe, HCl
(2) ⁻OH
NH2
CH3
p-toluidine
2 Br2
NH2
Br
Br
CH3
(1) NaNO2, HCl
(2) H3PO2
H
Br
Br
CH3
deaminated

Sales de arildiazonio – Rx de acoplamiento

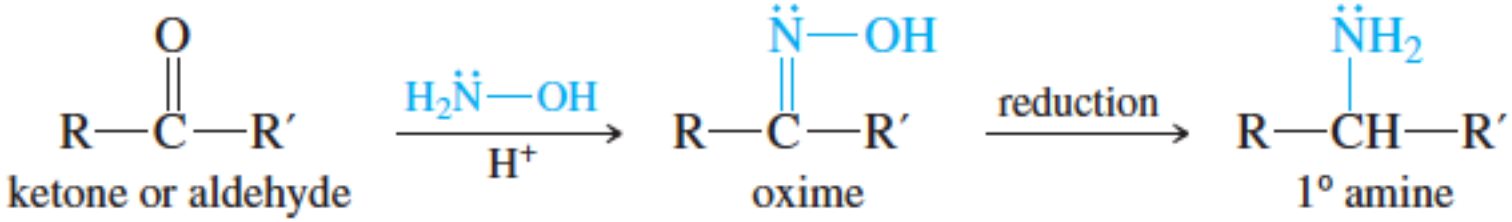


Mecanismo Acoplamiento diazoico

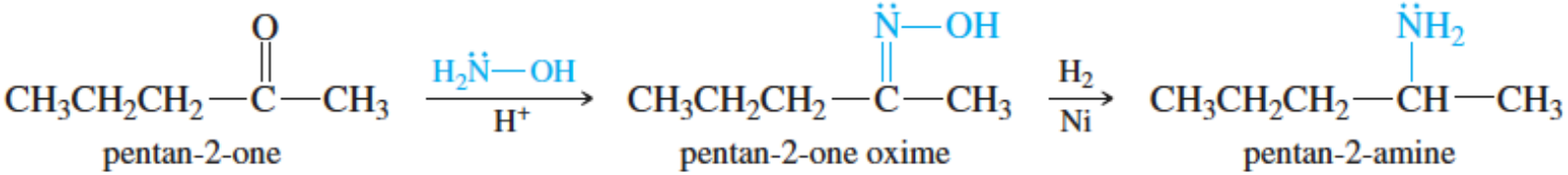


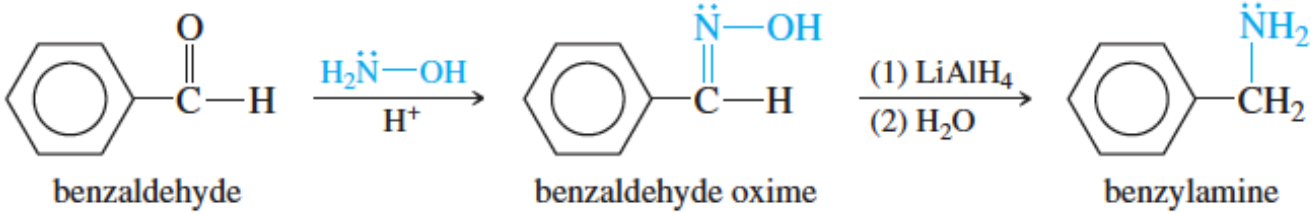


Síntesis de aminas vía aminación reductiva

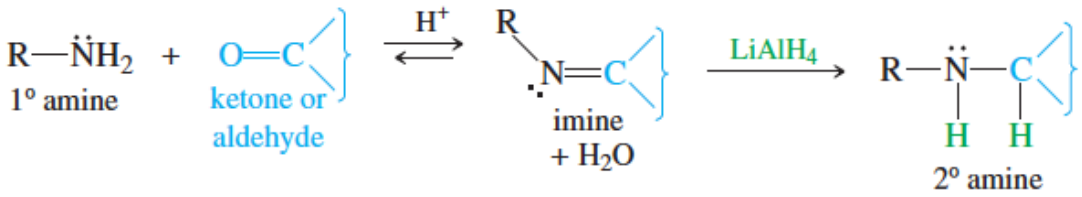


Examples

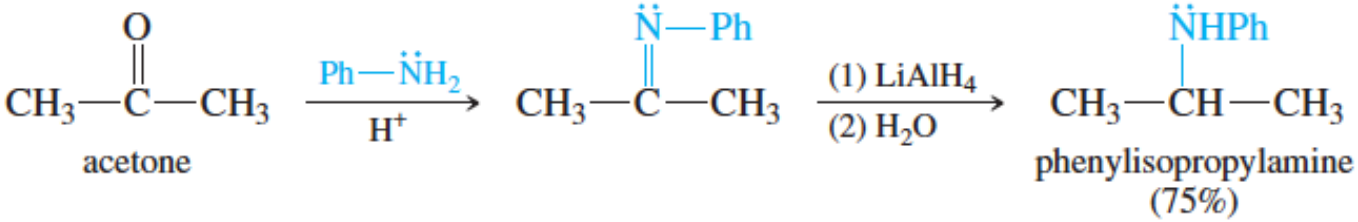




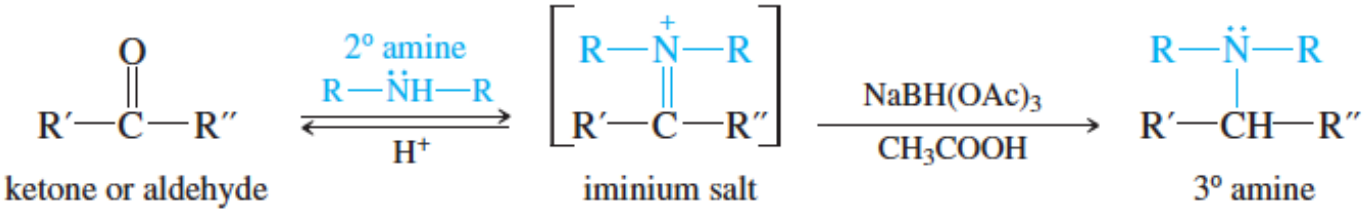
Síntesis de aminas vía aminación reductiva

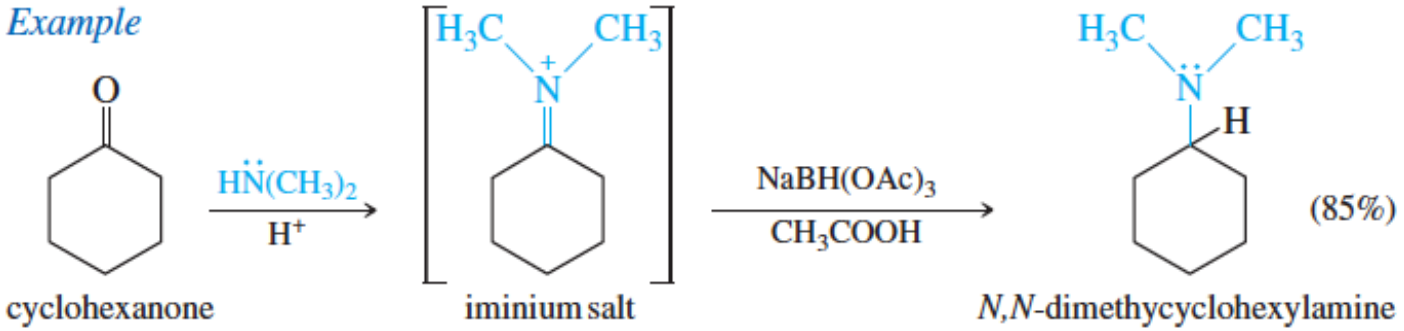


Example



Síntesis de aminas vía aminación reductiva





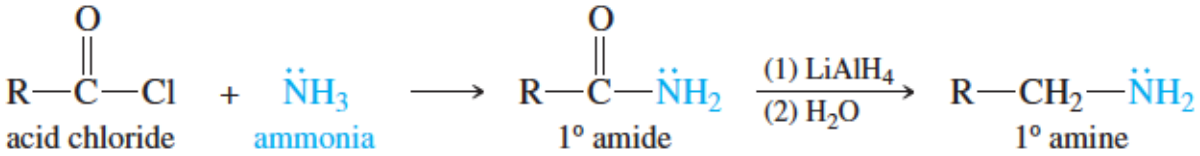
ejercicios

Show how to synthesize the following amines from the indicated starting materials.

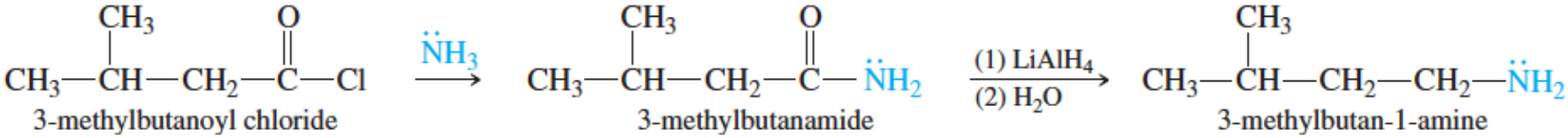
(a) *N*-cyclopentylaniline from aniline **(b)** *N*-ethylpyrrolidine from pyrrolidine

Síntesis de aminas vía acilación - reducción

Primary amines

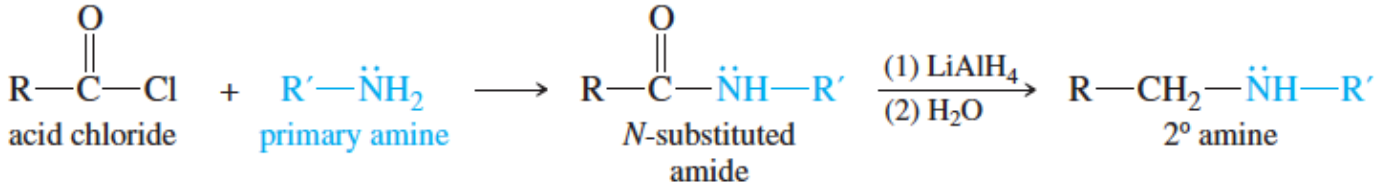


Example

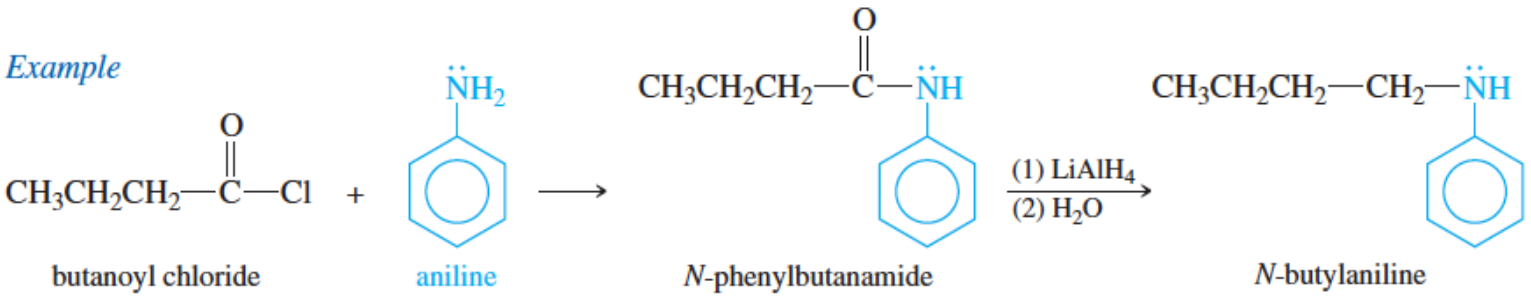


Síntesis de aminas vía acilación - reducción

Secondary amines

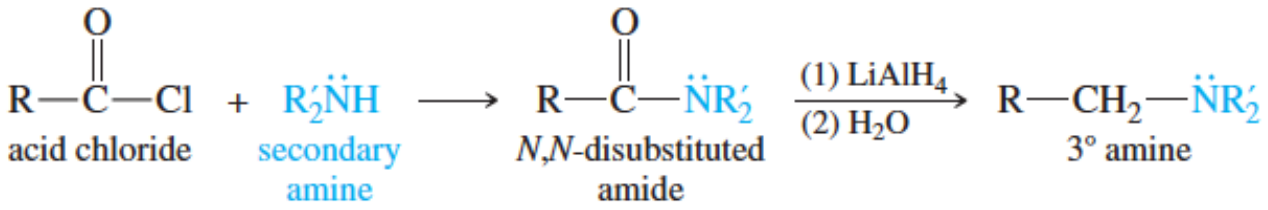


Example

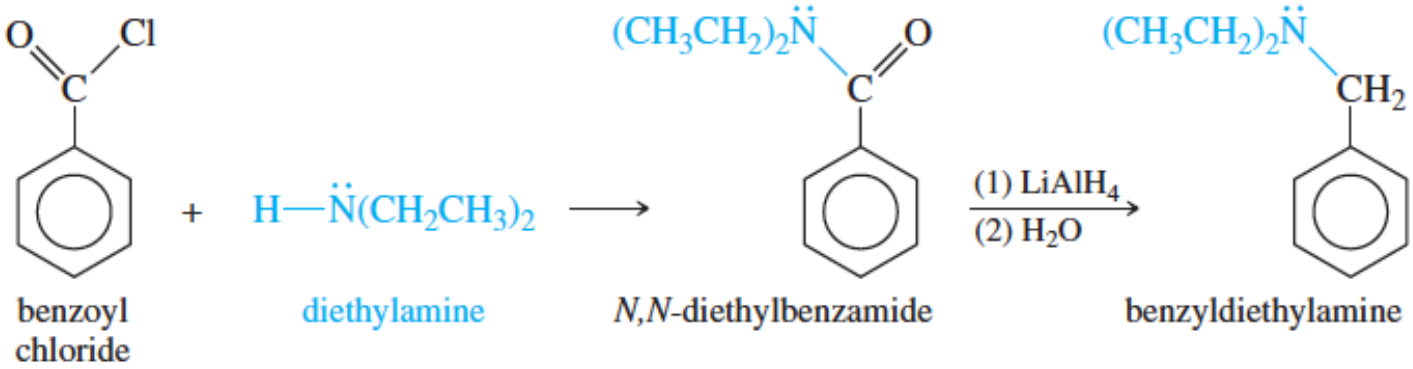


Síntesis de aminas vía acilación - reducción

Tertiary amines

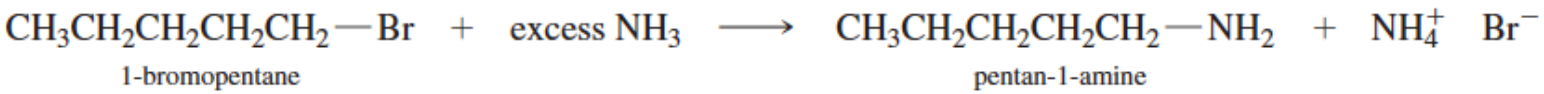


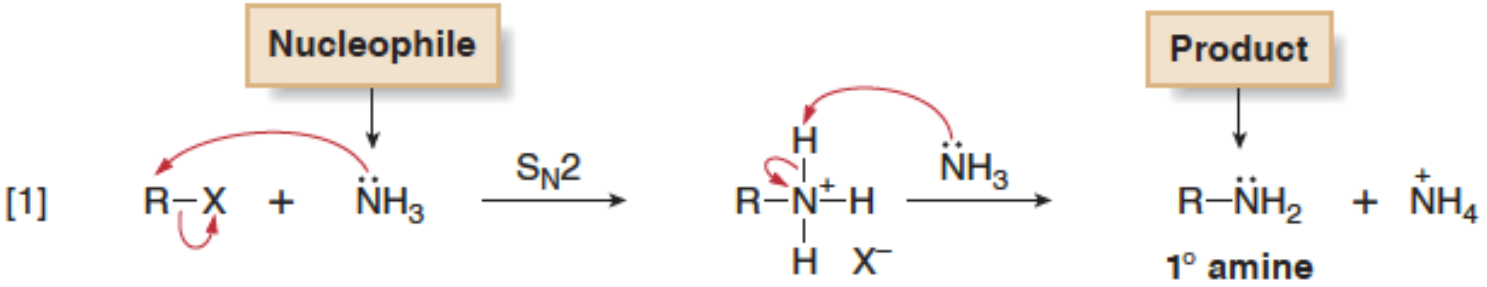
Example



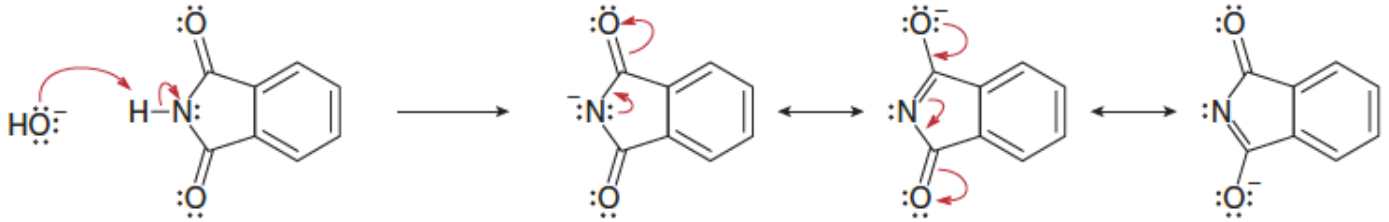
Síntesis de aminas primarias – alquilación directa

Example





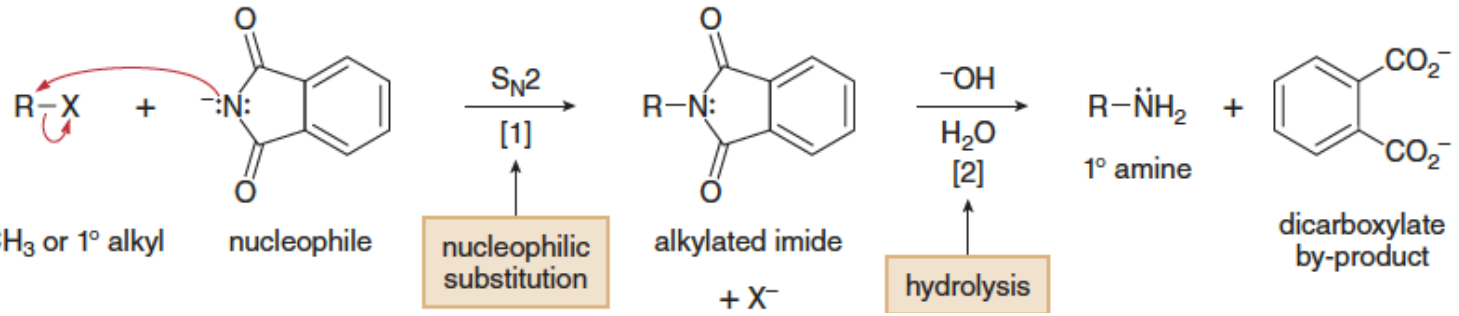
Síntesis de aminas primarias – Síntesis de Gabriel (1887)



phthalimide
$pK_a = 10$

resonance-stabilized anion

Steps in the Gabriel synthesis



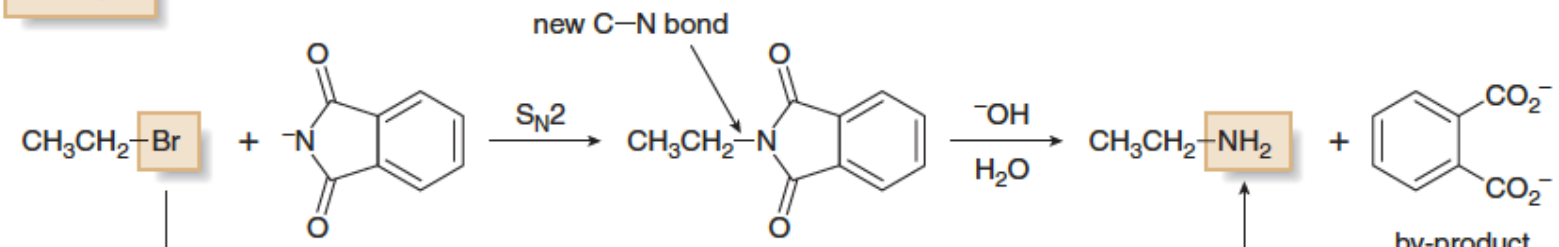
$R = CH_3$ or 1° alkyl

nucleophile

alkylated imide
$+ X^-$

dicarboxylate by-product

Example

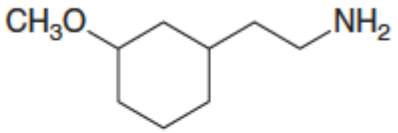


Ejercicios

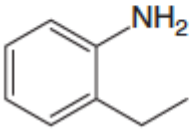
What alkyl halide is needed to prepare each 1° amine by a Gabriel synthesis?

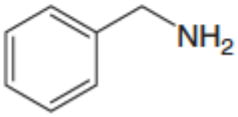
a. 

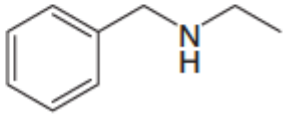
b. $(CH_3)_2CHCH_2CH_2NH_2$

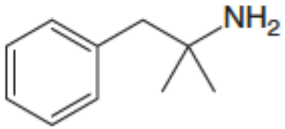
c. 

Which amines cannot be prepared by a Gabriel synthesis? Explain your choices.

a. 

b. 

c. 

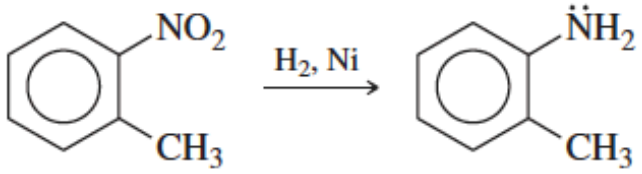
d. 

Síntesis de aminas primarias – reducción de otros grupos funcionales

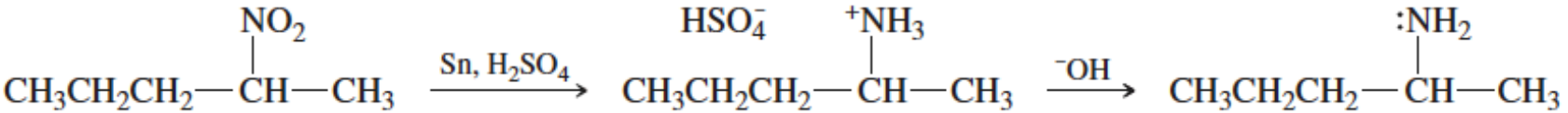
Nitro groups are reduced to 1° amines using a variety of reducing agents.

$$R{-}NO_2 \xrightarrow[\text{or}\ \text{Fe, HCl}\ \text{or}\ \text{Sn, HCl}]{H_2,\ \text{Pd-C}} R{-}NH_2 \quad (1^\circ\ \text{amine})$$

Examples



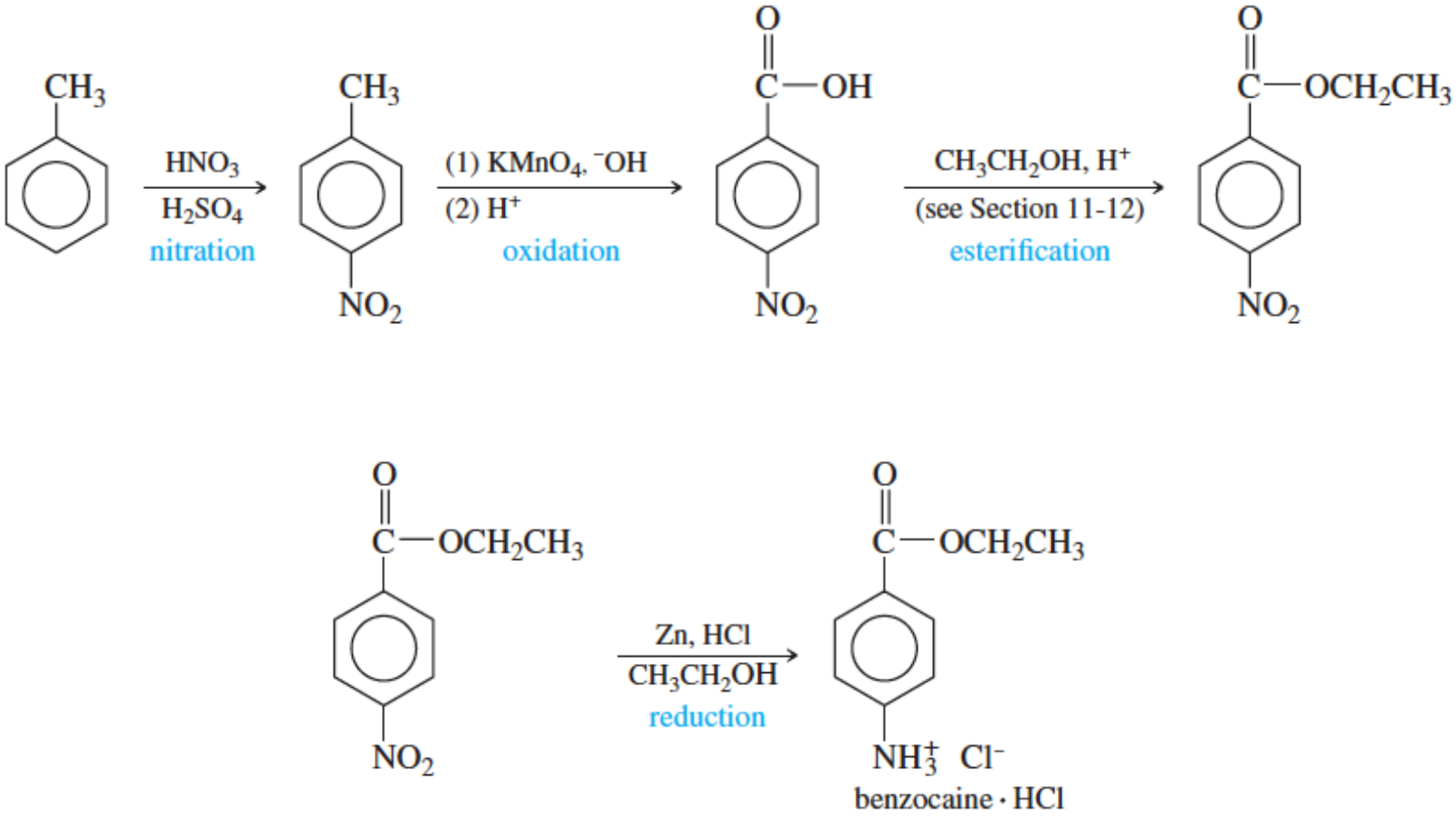
o-nitrotoluene → *o*-toluidine (90%)



2-nitropentane → 2-aminopentane (85%)

$$Ar{-}H \xrightarrow{HNO_3,\ H_2SO_4} Ar{-}NO_2 \xrightarrow{\text{reduction}} Ar{-}NH_2$$

Síntesis de aminas primarias – reducción de otros grupos funcionales



Síntesis de aminas primarias – reducción de otros grupos funcionales

Nitriles are reduced to 1° amines with $LiAlH_4$.

$$R{-}C{\equiv}N \xrightarrow[[2]\ H_2O]{[1]\ LiAlH_4} R{-}CH_2NH_2$$

1° amine

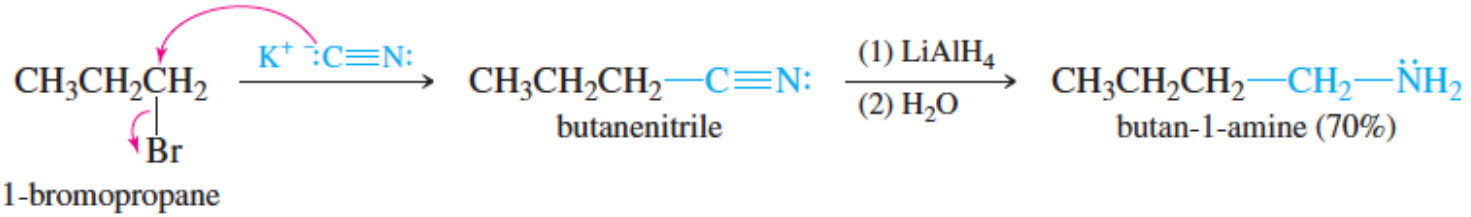
Example

$$CH_3{-}Br \xrightarrow[S_N2]{NaCN} CH_3{-}C{\equiv}N \xrightarrow[[2]\ H_2O]{[1]\ LiAlH_4} CH_3{-}CH_2NH_2$$

new C–C bond

1° amine

Example



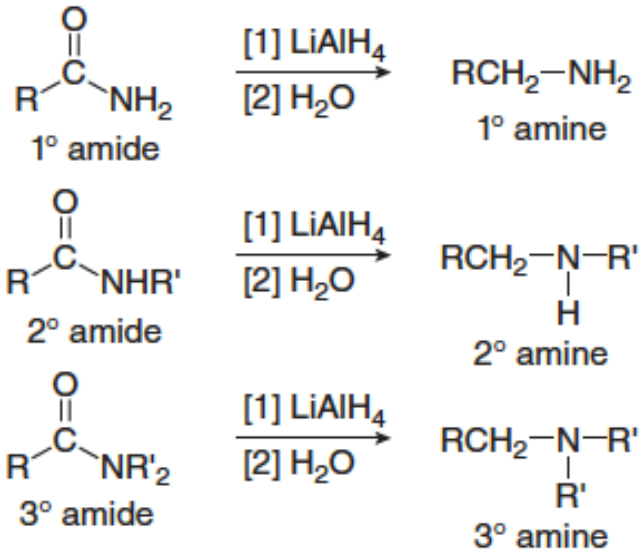
1-bromopropane

butanenitrile

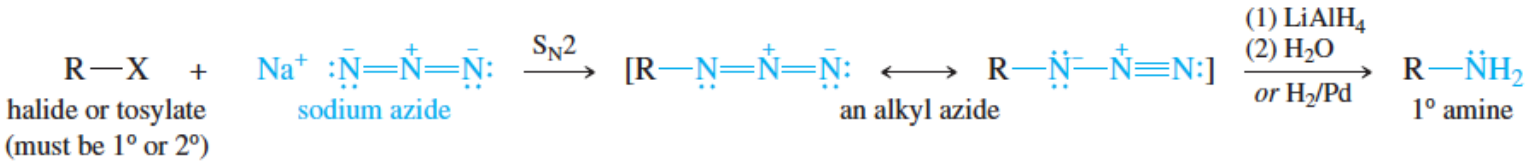
butan-1-amine (70%)

Síntesis de aminas – reducción de otros grupos funcionales

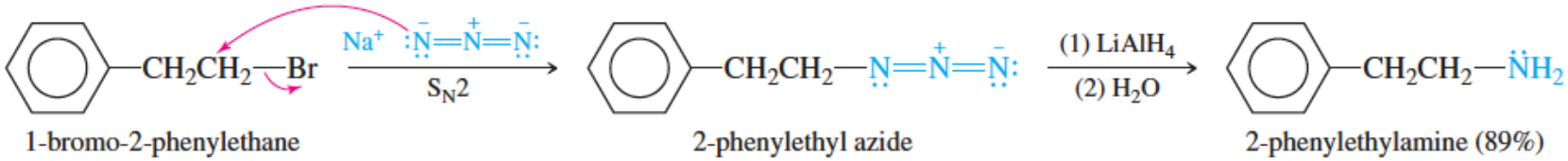
Primary (1°), 2°, and 3° amides are reduced to 1°, 2°, and 3° amines, respectively, by using $LiAlH_4$.



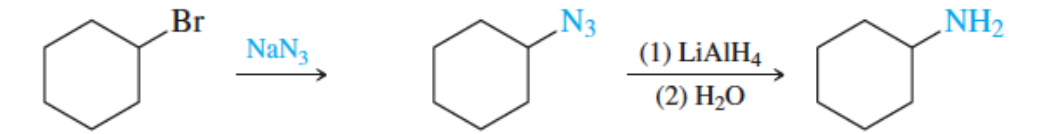
Síntesis de aminas – reducción de otros grupos funcionales



Examples



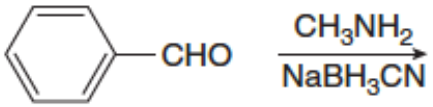
1-bromo-2-phenylethane — 2-phenylethyl azide — 2-phenylethylamine (89%)

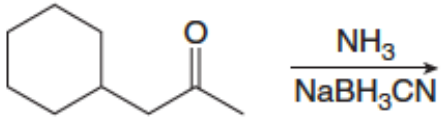


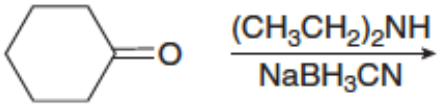
cyclohexyl bromide — cyclohexyl azide — cyclohexylamine (54%)

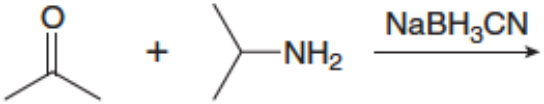
ejercicios

Draw the product of each reaction.

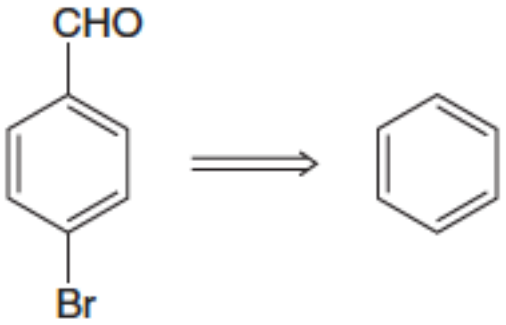
a. 

b. 

c. 

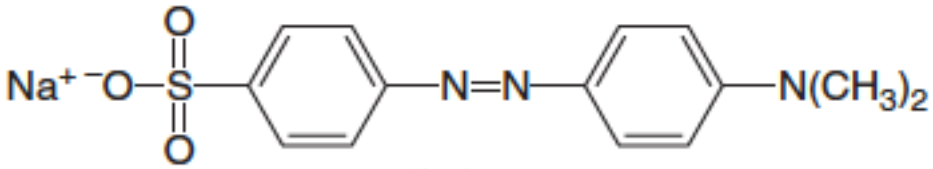
d. 

ejercicios



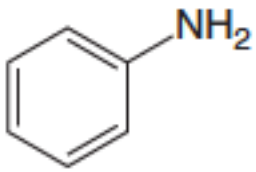
ejercicios

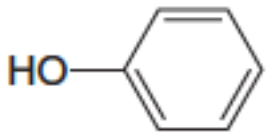
Cuáles son los materiales de partida para sintetizar el siguiente indicador?



methyl orange
an orange dye

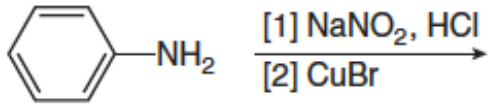
Dibuje los productos cuando cada uno reacciona con $C_6H_5N_2^+Cl^-$

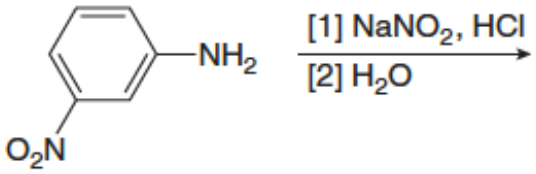
a. 

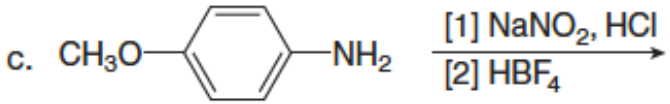
b. 

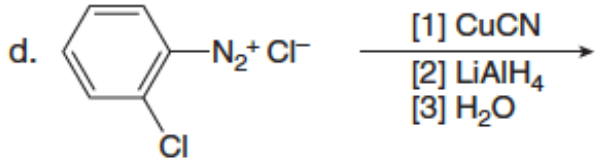
c. 

ejercicios

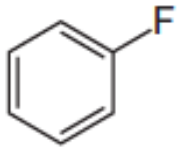
a. 

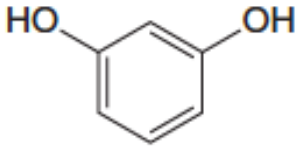
b. 

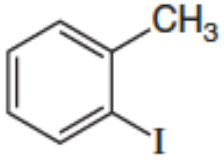
c. 

d. 

A partir de benceno

a. 

b. 

c. 

d.