

# Pirrol, furano y tiofeno

Heterociclos aromáticos monoatómicos de cinco miembros

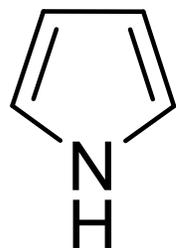
\*Propiedades químicas generales y particulares

Síntesis orgánica

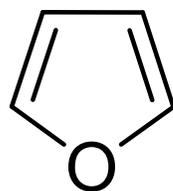
\*Reacciones principales: Mannich (amino-metilación), acilación, alquilación, metalación en  $C\alpha$  y en  $1H$  de  $NH$ , sulfonilación, carboxilación, halogenación, sustitución electrofílica aromática (SEA).

Importancia y formación en alimentos.

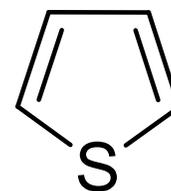
# Pirrol, furano y tiofeno



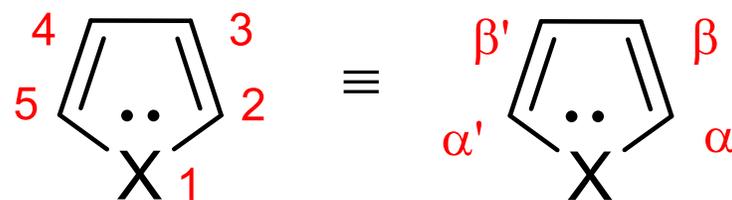
pirrol



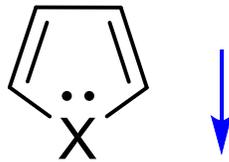
furano



tiofeno



# Propiedades electrónicas y estructuras resonantes

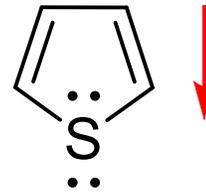
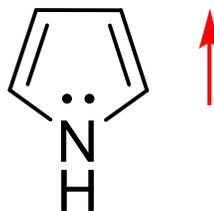
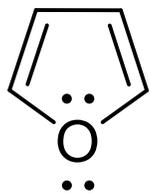


Distribución desigual  
de los e-

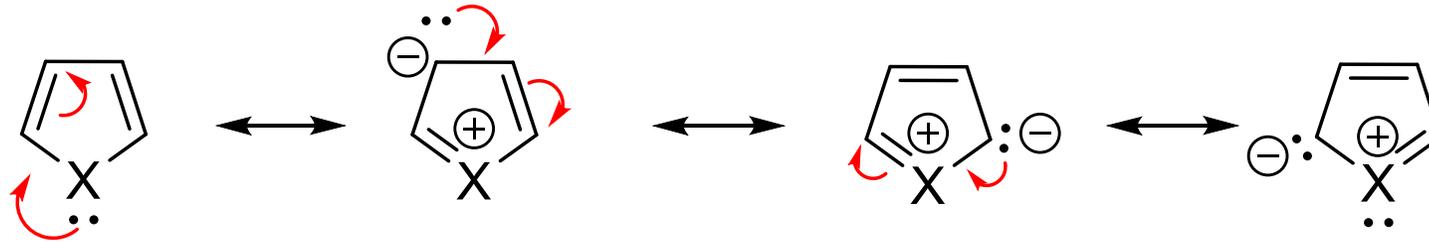


En general, limitada  
disponibilidad  
de e-

Momento dipolar

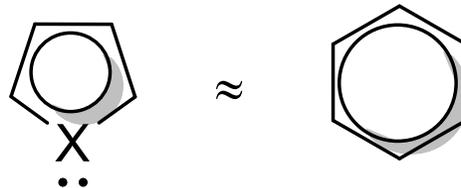


# Estructuras resonantes



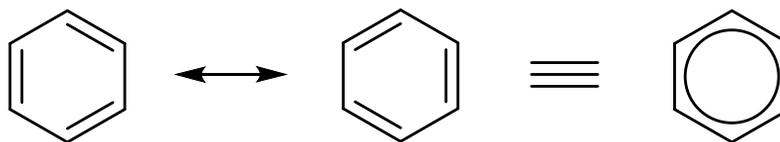
Donde X = NH, NR, O, S.

Resonancia  $\pi$  en un sistema plano

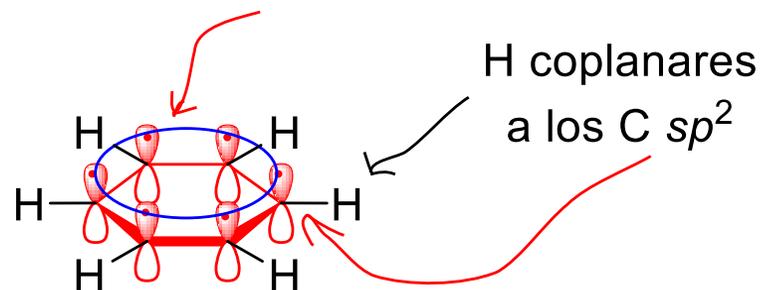


# Aromaticidad

- Sistemas cíclicos planos con electrones  $\pi$  deslocalizados
- Regla de Hückel,  $4n + 2$ , donde  $n =$  número entero

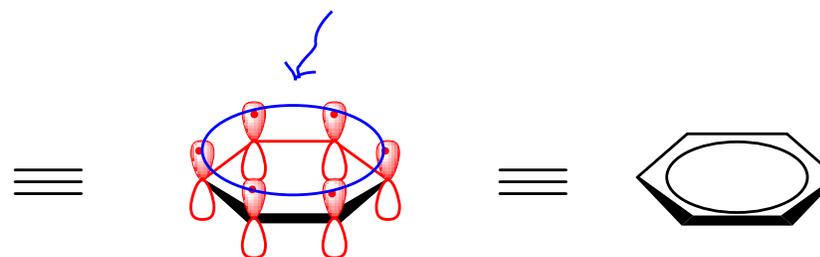


Orbitales  $p$  perpendiculares al plano del anillo



Los C son equidistantes

electrones  $\pi$  deslocalizados



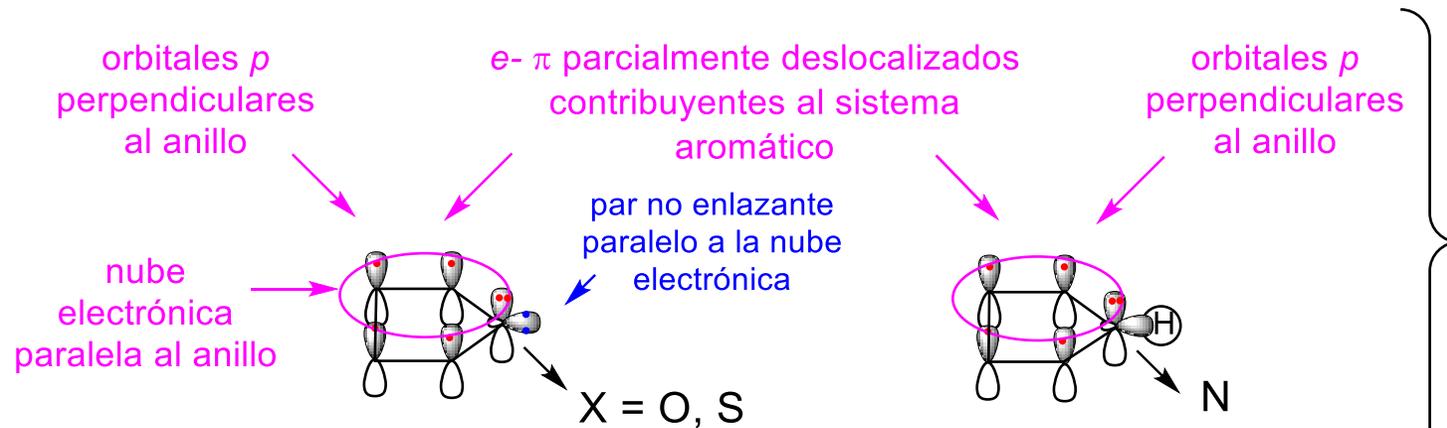
Hay seis e- distribuidos en seis átomos

La deslocalización de e- es homogénea por ser un homociclo

# Aromaticidad

## Heterociclos de cinco miembros con un heteroátomo

Estructura electrónica

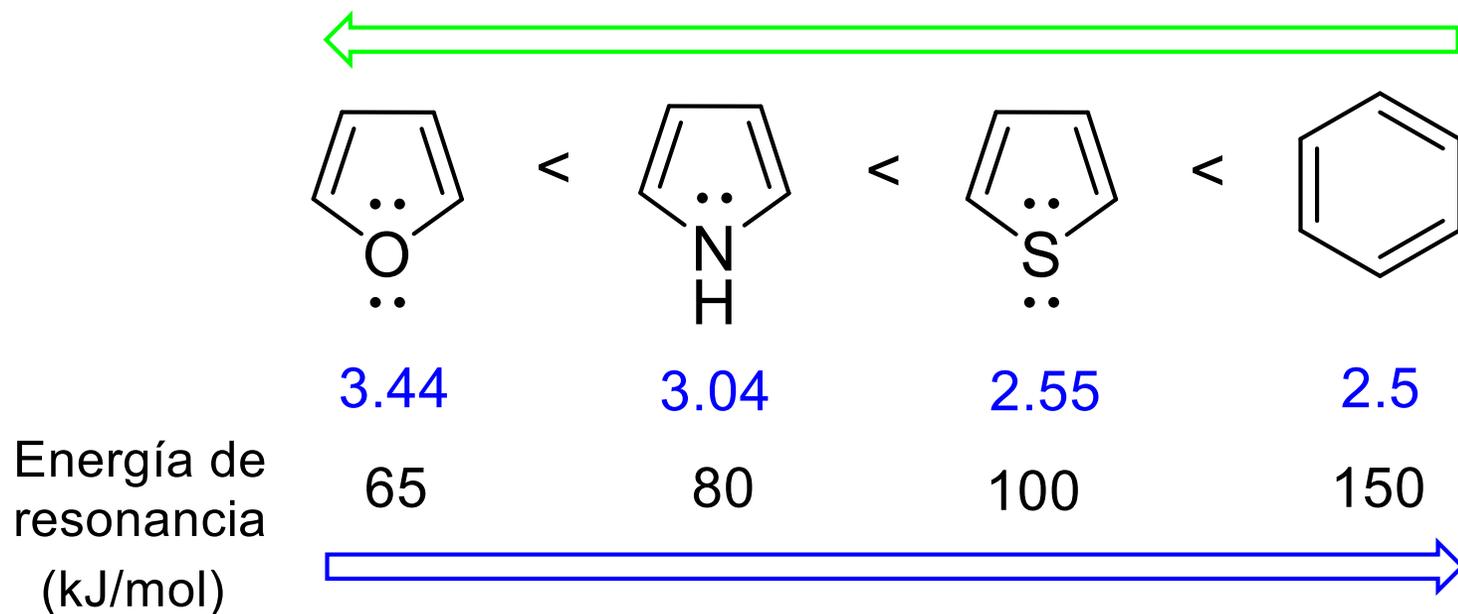


Son muy reactivos, hay seis  $e^-$  repartidos en cinco átomos, son  $\pi$  excedentes

A mayor electronegatividad ( $O > N > S$ ), menor deslocalización electrónica anular y menor carácter aromático

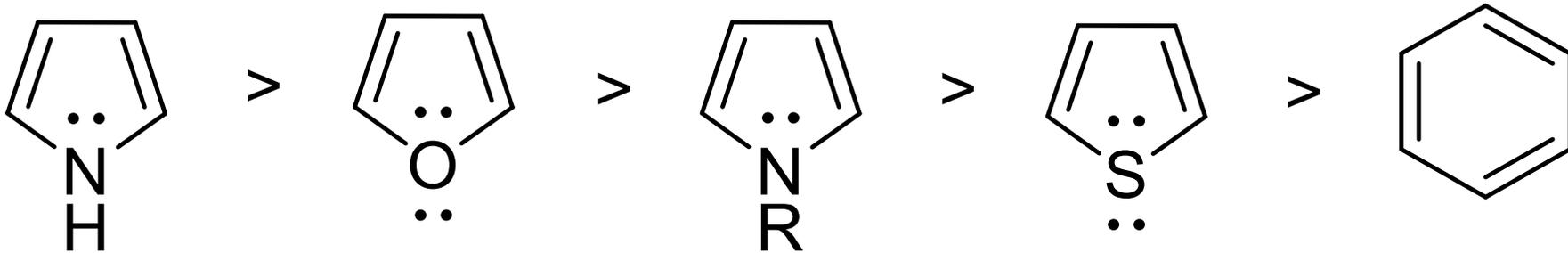
# Aromaticidad = Estabilidad por conjugación, alta energía de resonancia

*A mayor electronegatividad,  
menor aromaticidad*



*A menor diferencia de electronegatividad,  
y mayor energía de resonancia, mayor aromaticidad*

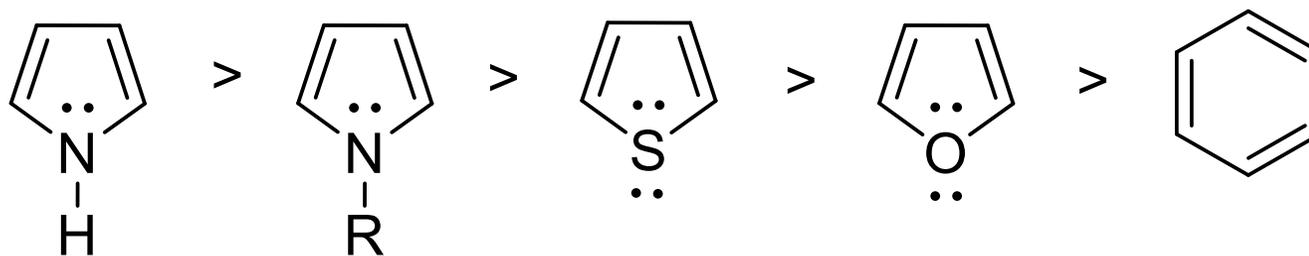
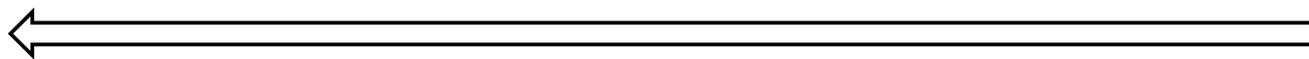
# Reactividad nucleofílica



Además de la electronegatividad, en la reactividad influyen las propiedades ácidas y el comportamiento como dieno.

# Reacciones de SEA

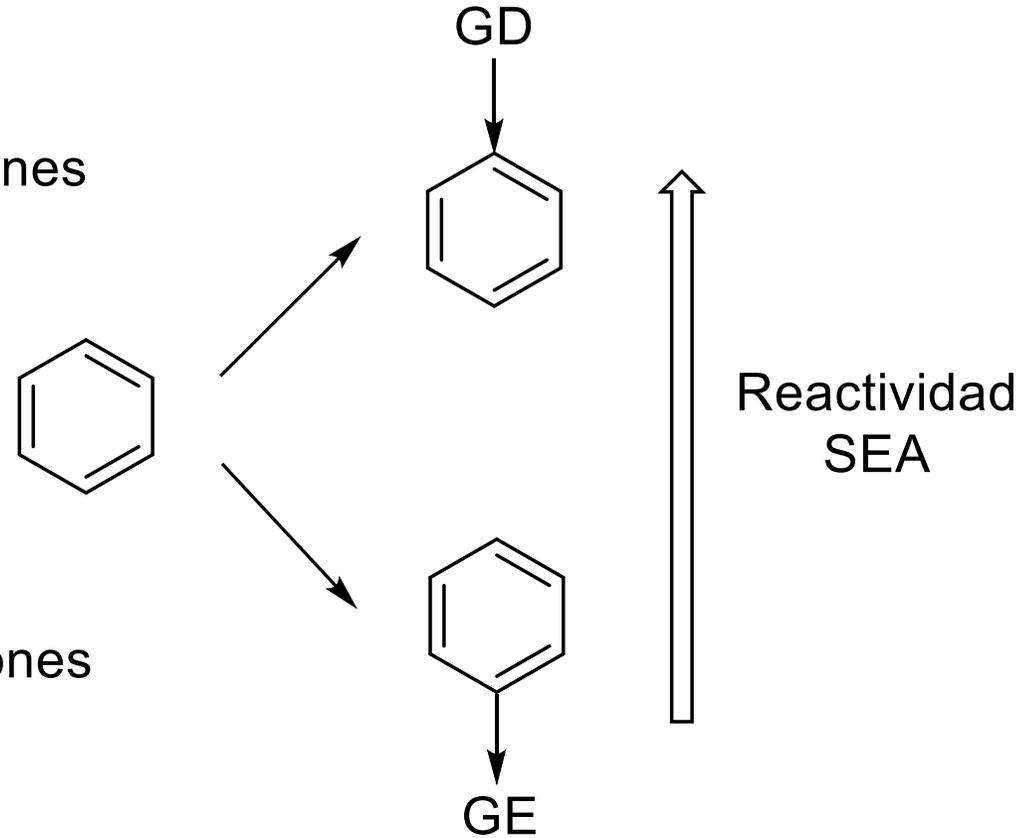
Reactividad como  
SEA



# Reactividad por SEA

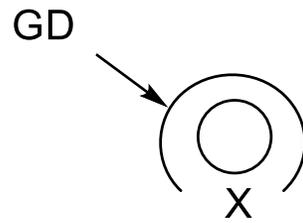
GD= Grupos donadores de electrones

GE= Grupos sustractores de electrones

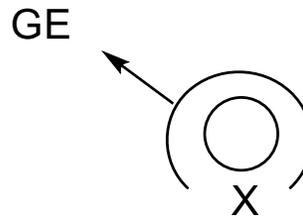
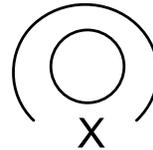


# Reactividad de aromáticos

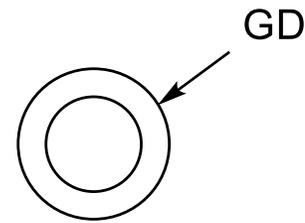
mayor reactividad  
por SEA



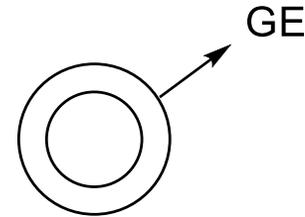
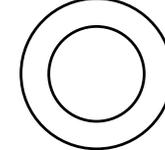
Heterociclo  
aromático



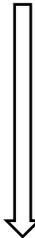
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Homociclo  
aromático



mayor reactividad  
por SNA

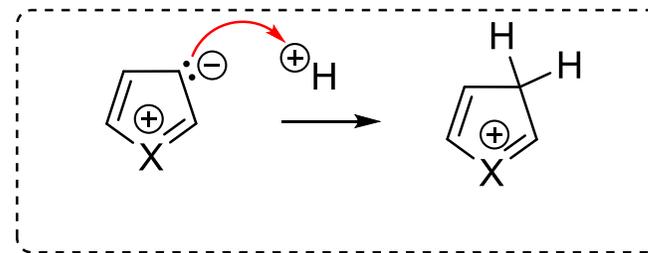
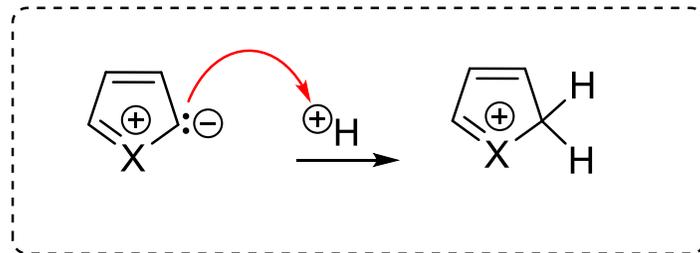
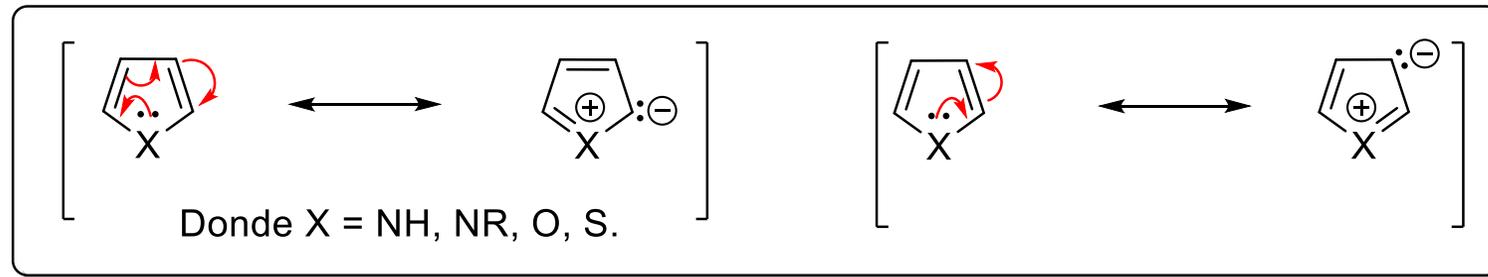


# Resonancia

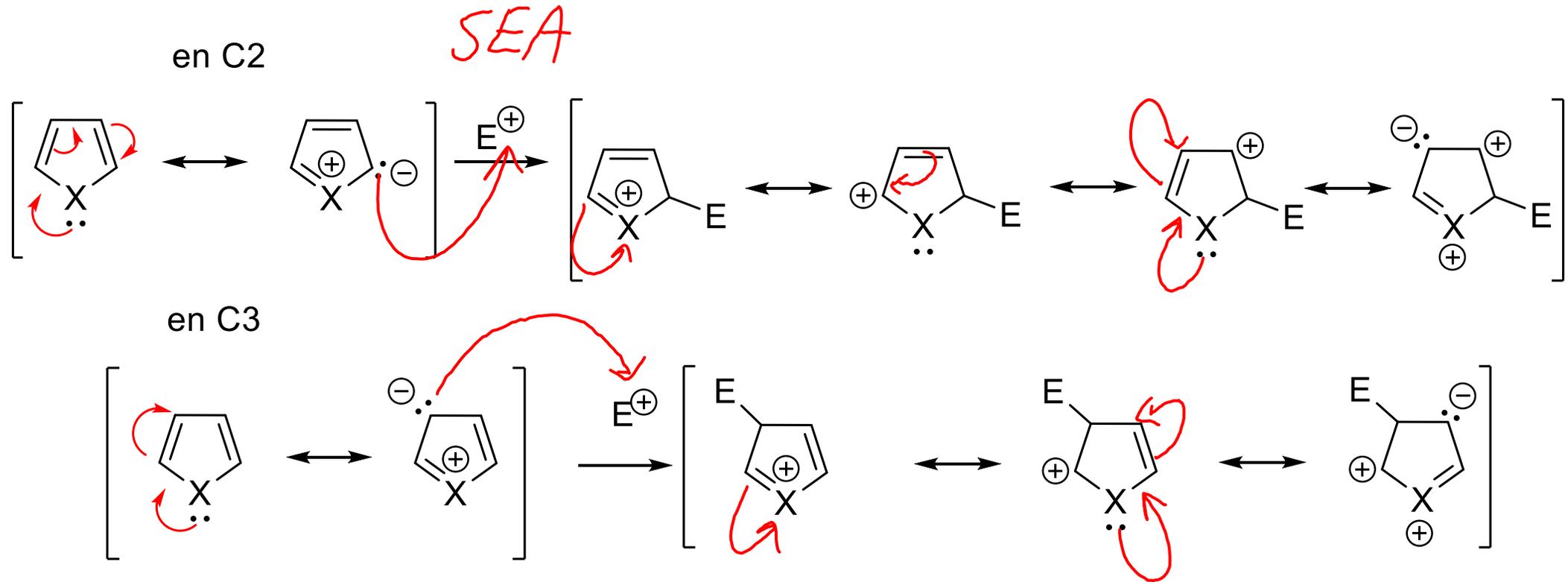
Considerando la resonancia del pirrol, furano y tiofeno, la SEA está muy favorecida en las posiciones 2 y 5 ( $\alpha$  y  $\alpha'$ ).

Eso explica en parte la elevada reactividad y polimerización del furano y el pirrol, ej., en alimentos ácidos.

## Resonancia

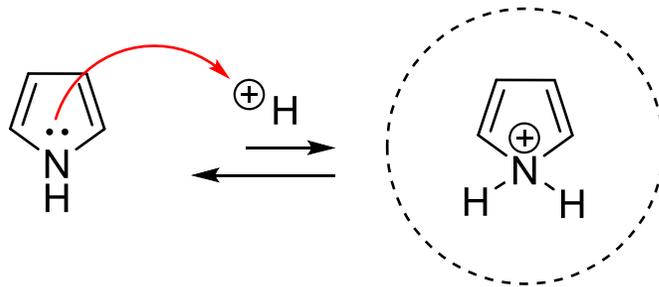
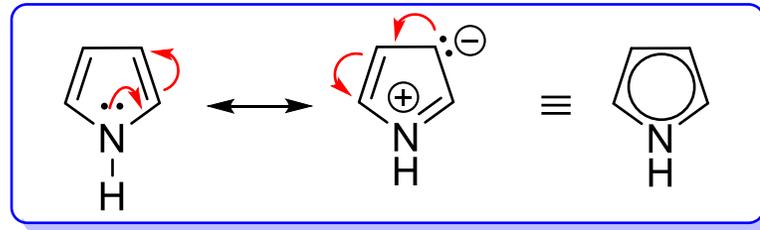


# Resonancia y SEA

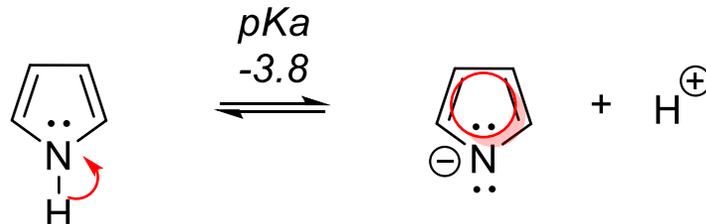


# Pirrol, propiedades químicas

El pirrol es muy poco básico debido a que el par de e<sup>-</sup> del N está comprometido en la estabilidad del sistema aromático. Por el contrario, se comporta como ácido y su 1H puede ser sustraído por bases fuertes.



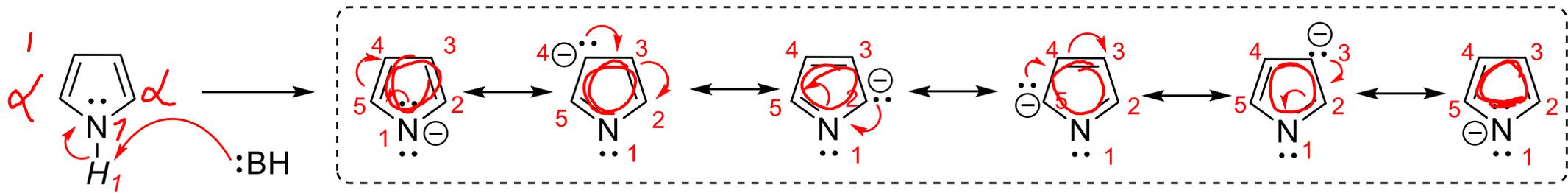
Estructura poco favorecida, se rompe el sexteto aromático y no presenta resonancia



*sexteto aromático presente*

# Pirrol, propiedades ácido-base y resonancia

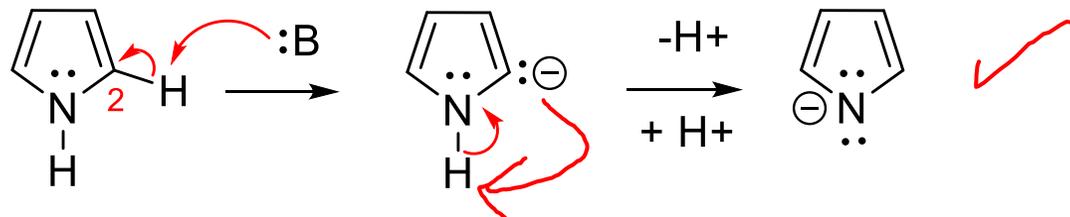
La sustracción del 1H pirrólico está muy favorecida debido a que el N retiene la carga -, se mantiene la aromaticidad y se producen estructuras resonantes que la conservan.



donde B =  $\text{NaNH}_2$ ,  $\text{NaH}$ ,  $\text{KH}$ ,  $\text{R-Mg-X}$ ,  $n\text{-BuLi}$ .

*Sodamida*

No obstante, el  $\text{H}^+$  que prácticamente se pierde es el de C2.



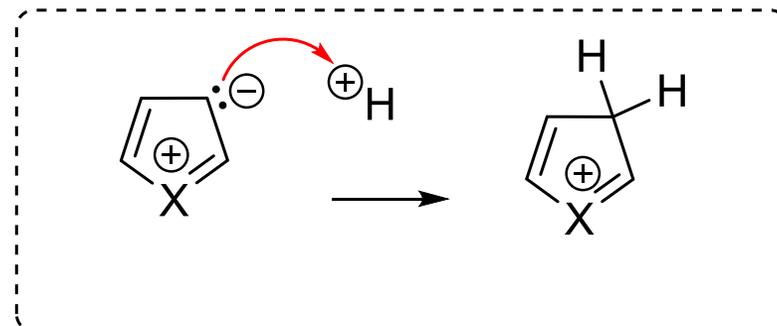
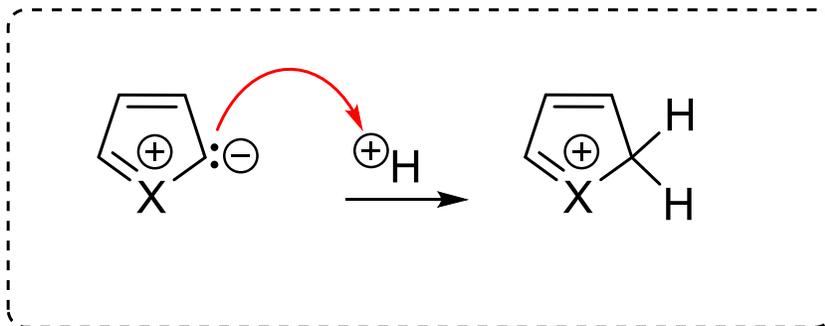
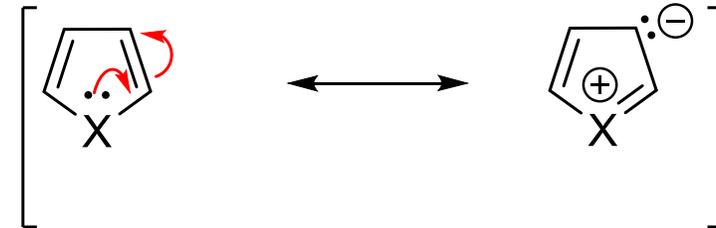
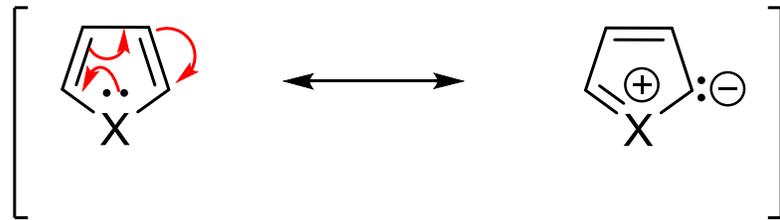
# Furano y pirrol:

## Algunas propiedades químicas particulares

### Reacciones en medio ácido

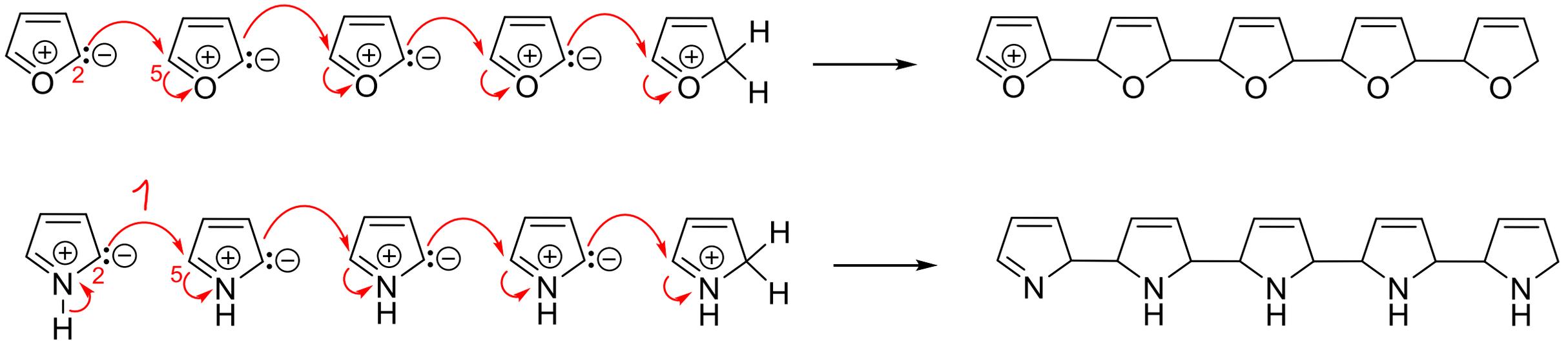
La reacción con ácidos fuertes en cantidades superiores a las catalíticas no implica la protonación del N o el O, sino su dimerización o polimerización:

*Nota: Para proponer la reactividad se debe plantear primero la deslocalización de los e<sup>-</sup>.*

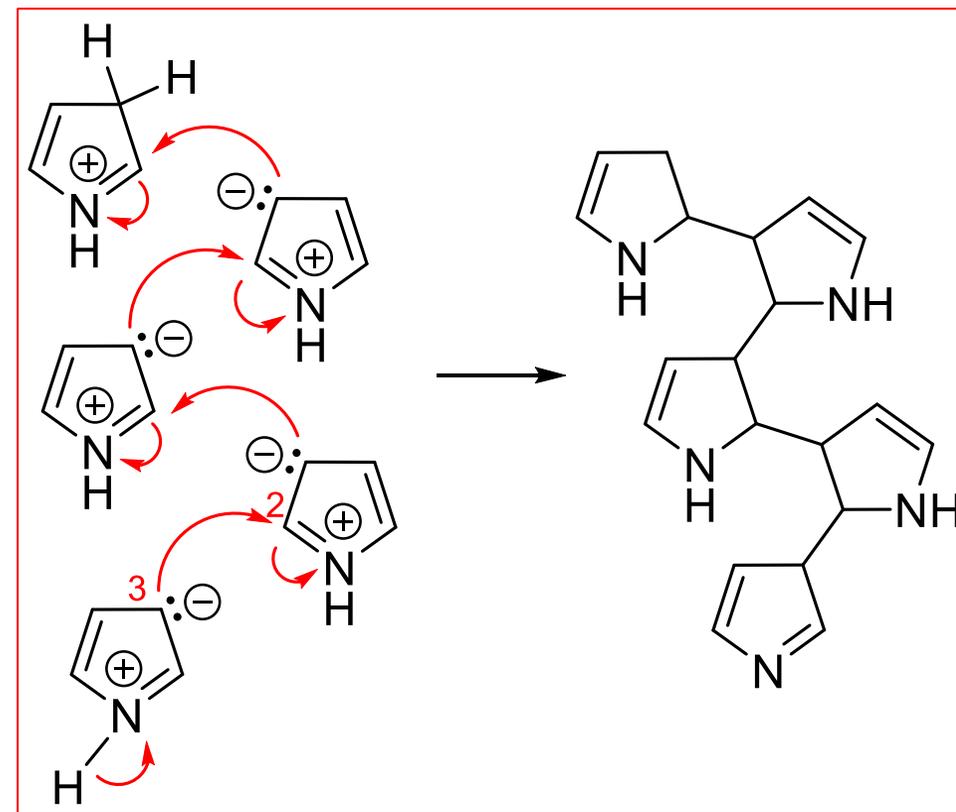
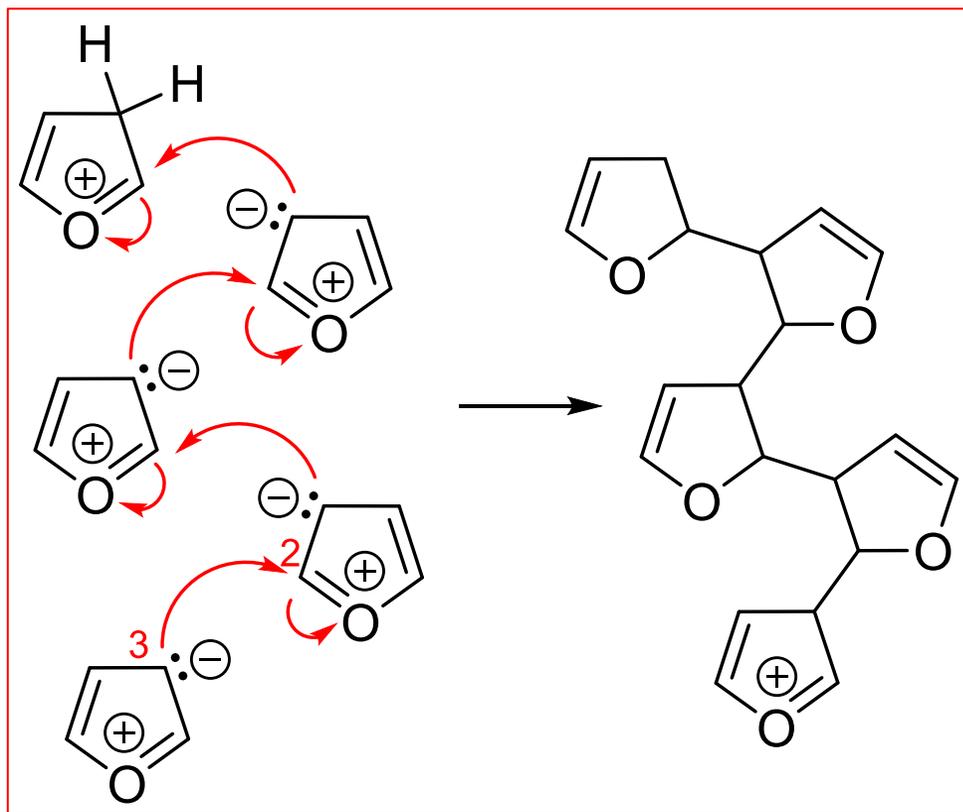


# Polimerización I del furano y pirrol

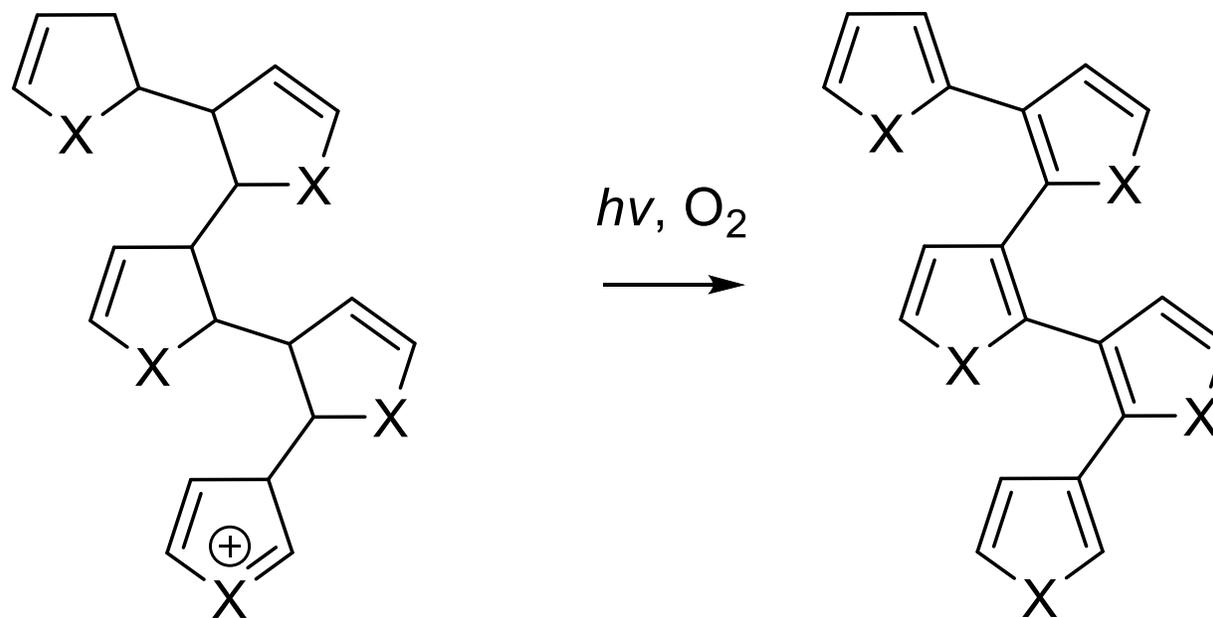
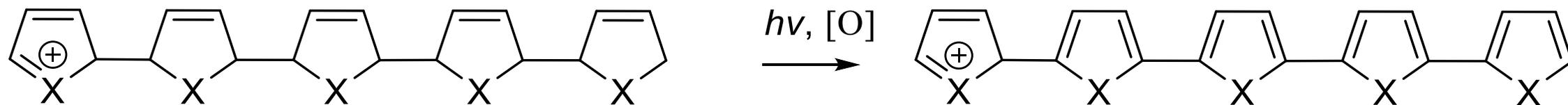
Así, en presencia de ácidos minerales, el pirrol y el furano se descomponen mediante reacciones de polimerización:



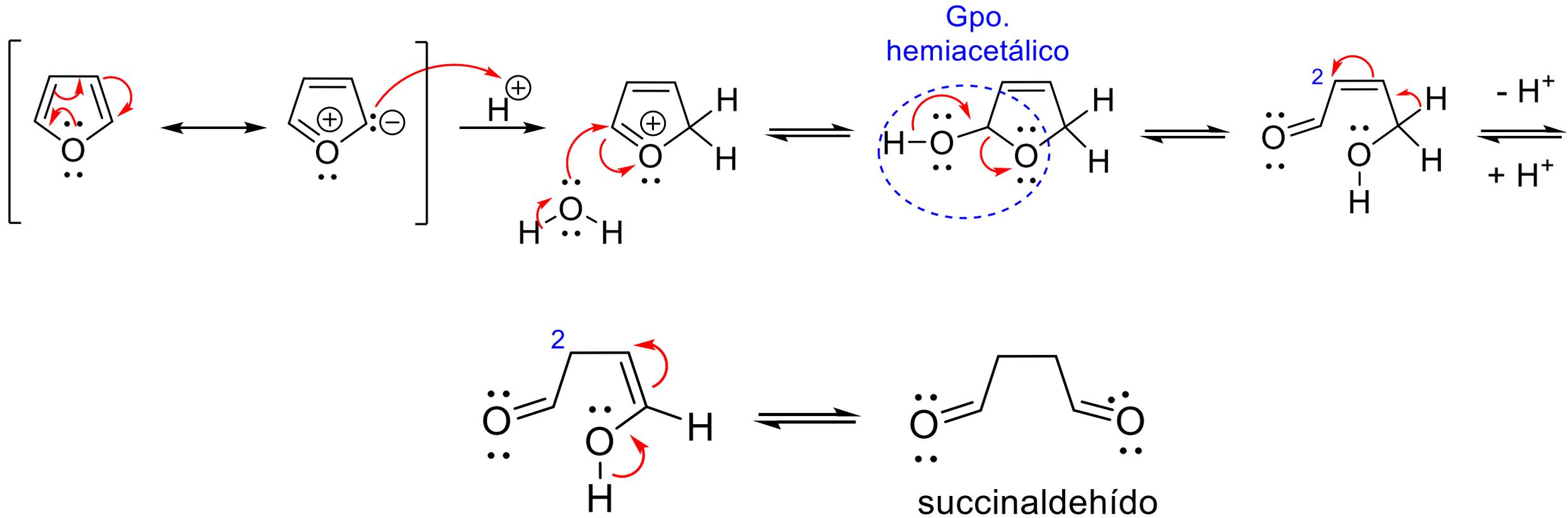
# Polimerización II del furano y pirrol



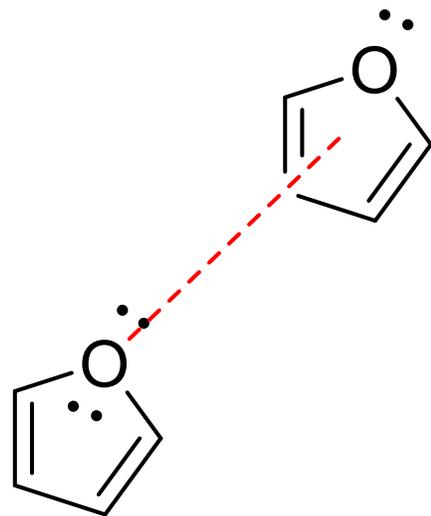
# Oxidación de las estructuras poliméricas



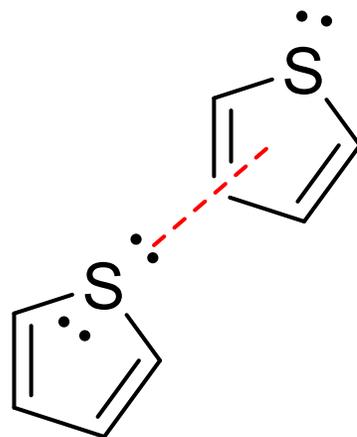
# Descomposición, reapertura del ciclo



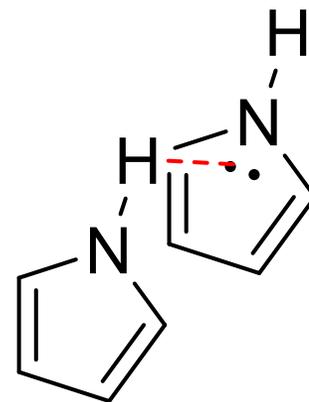
# Propiedades físicas



p.e. 31 °C



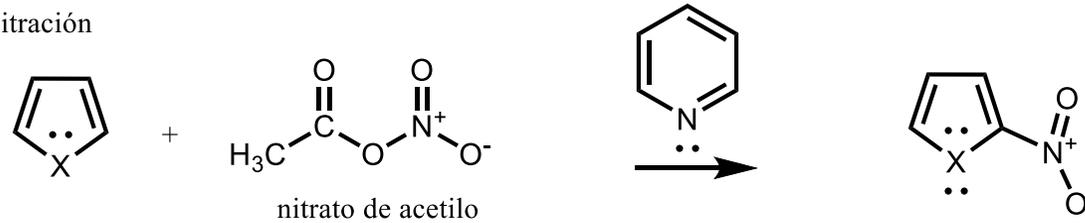
p.e. 84 °C



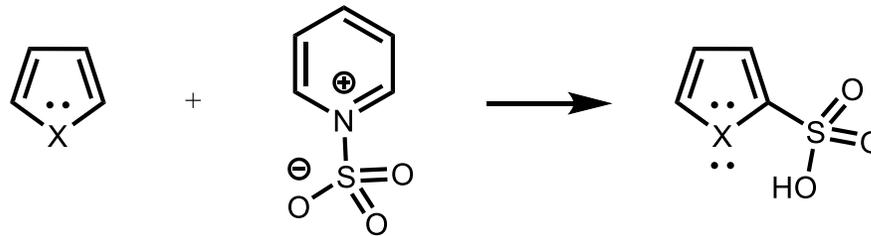
p.e. 129 °C

# Reacciones comunes de SEA

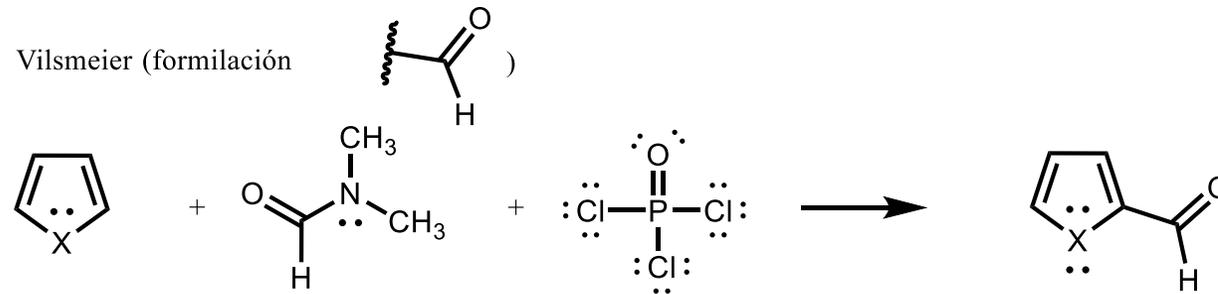
Nitración



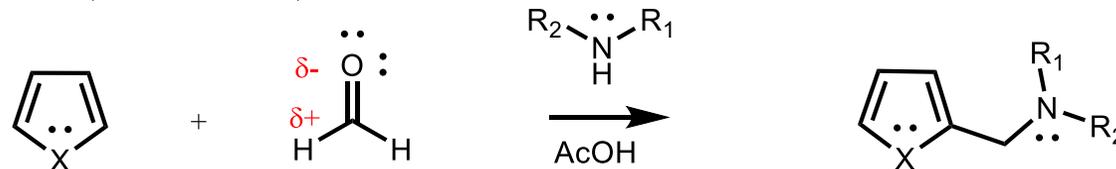
Sulfonación



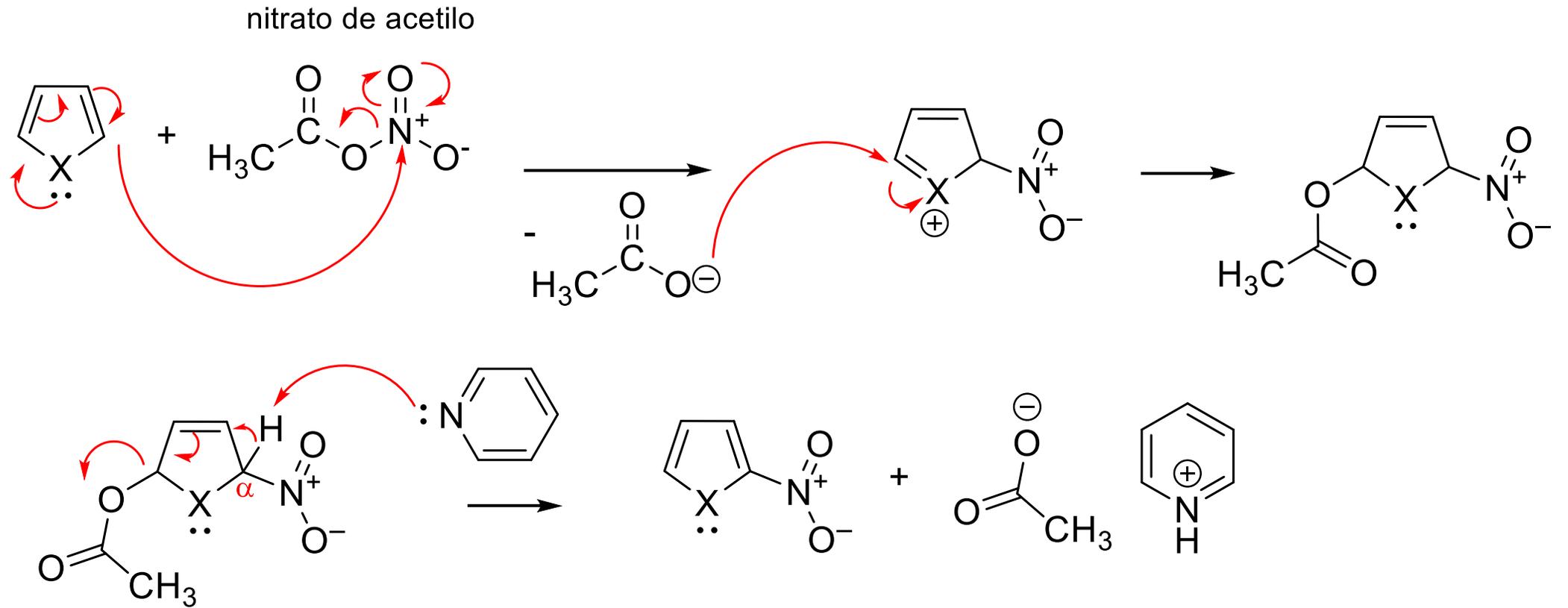
Vilsmeier (formilación)



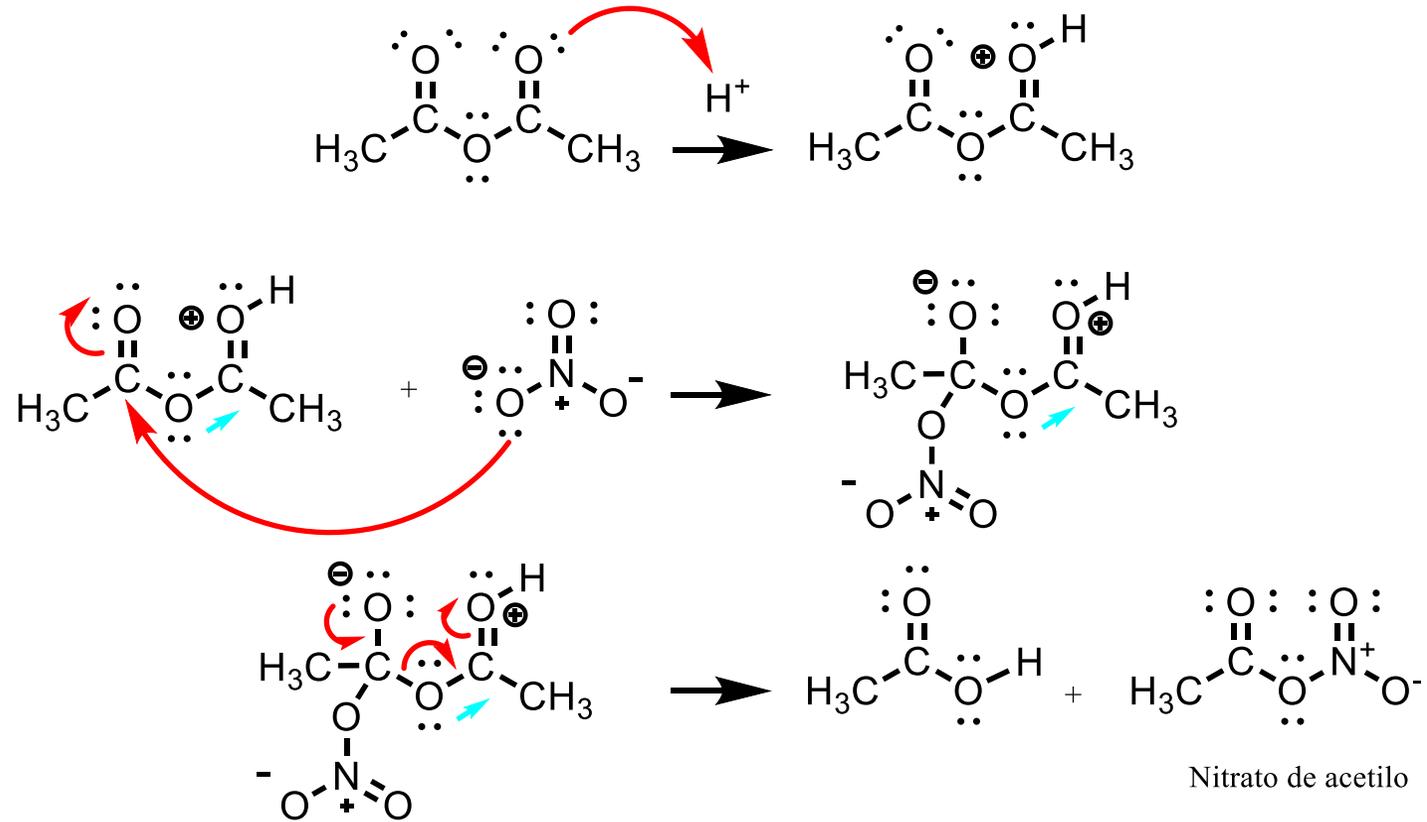
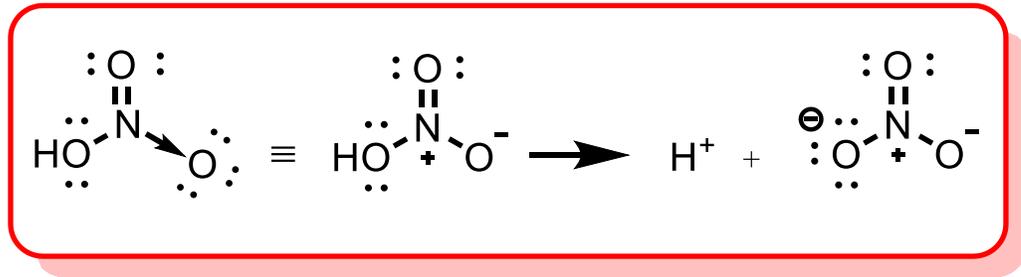
Mannich (aminometilación)



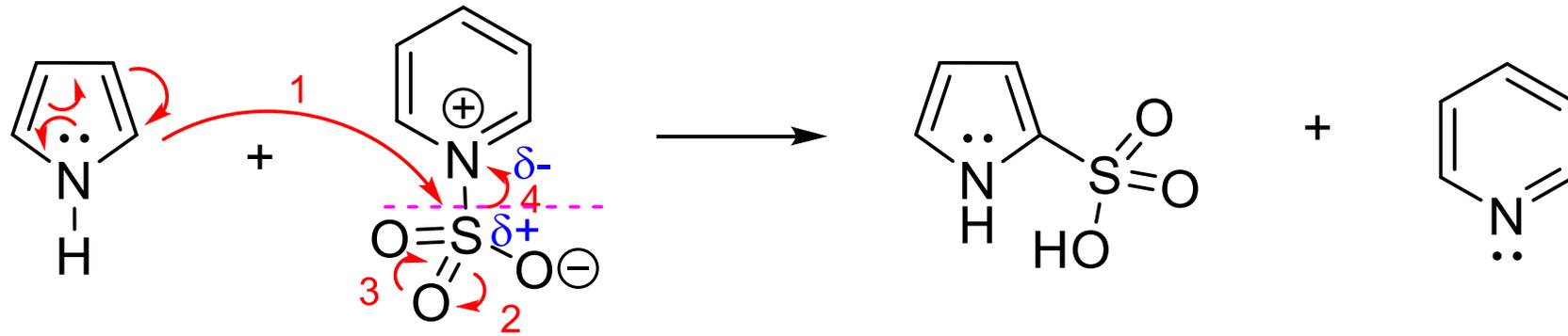
# Nitración-mecanismo



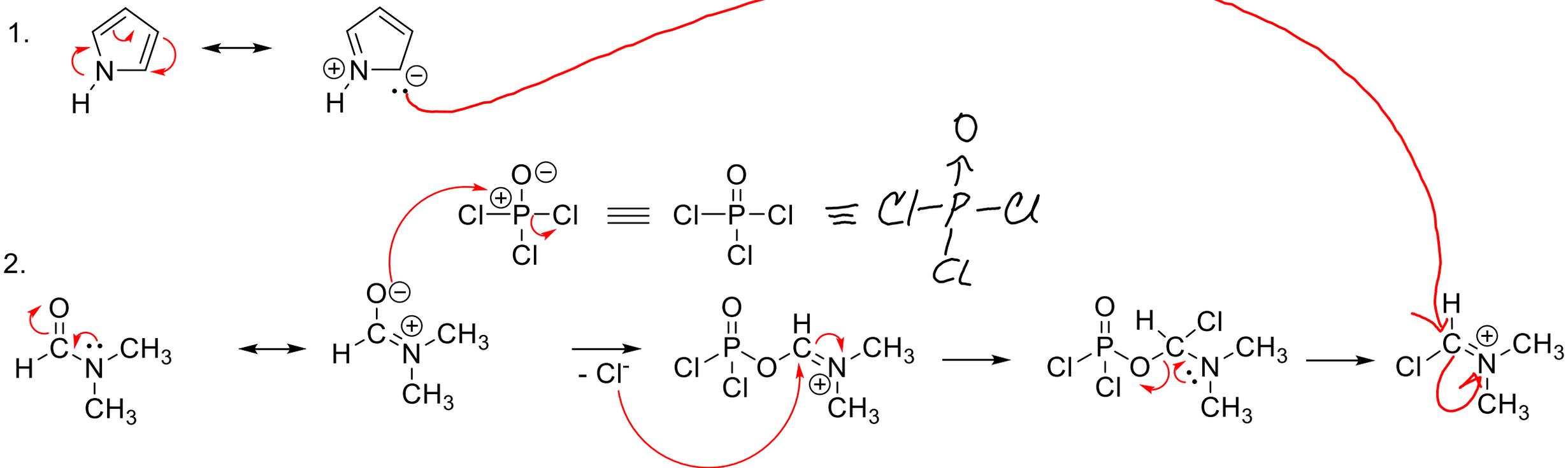
# Formación de nitrato de acetilo



# Sulfonación

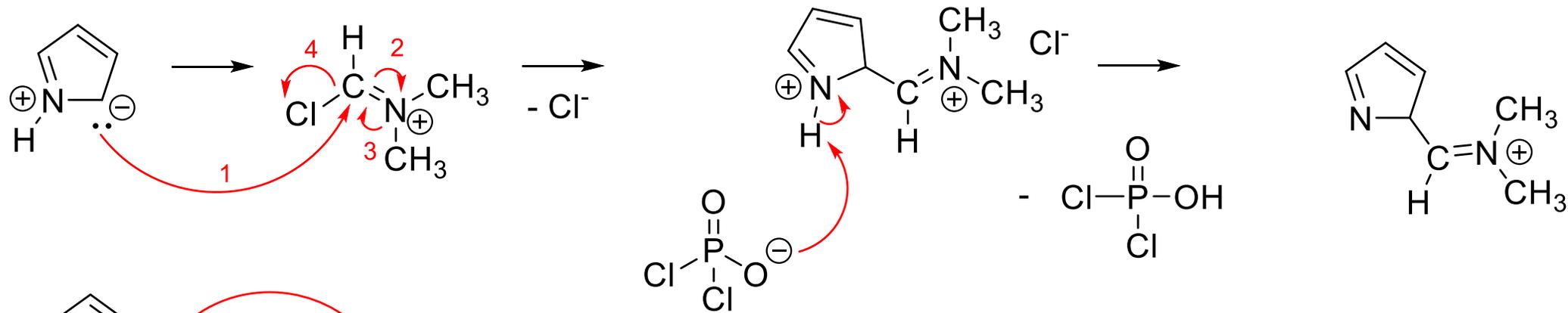


# Vilsmeier (formilación) → mecanismo

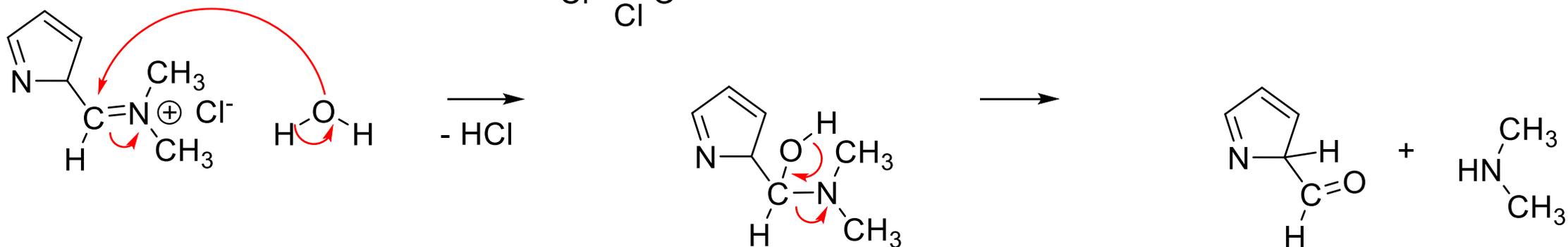


# Vilsmeier → mecanismo

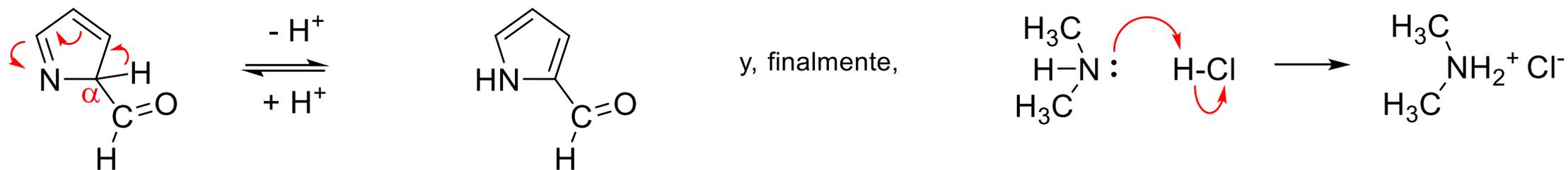
3.



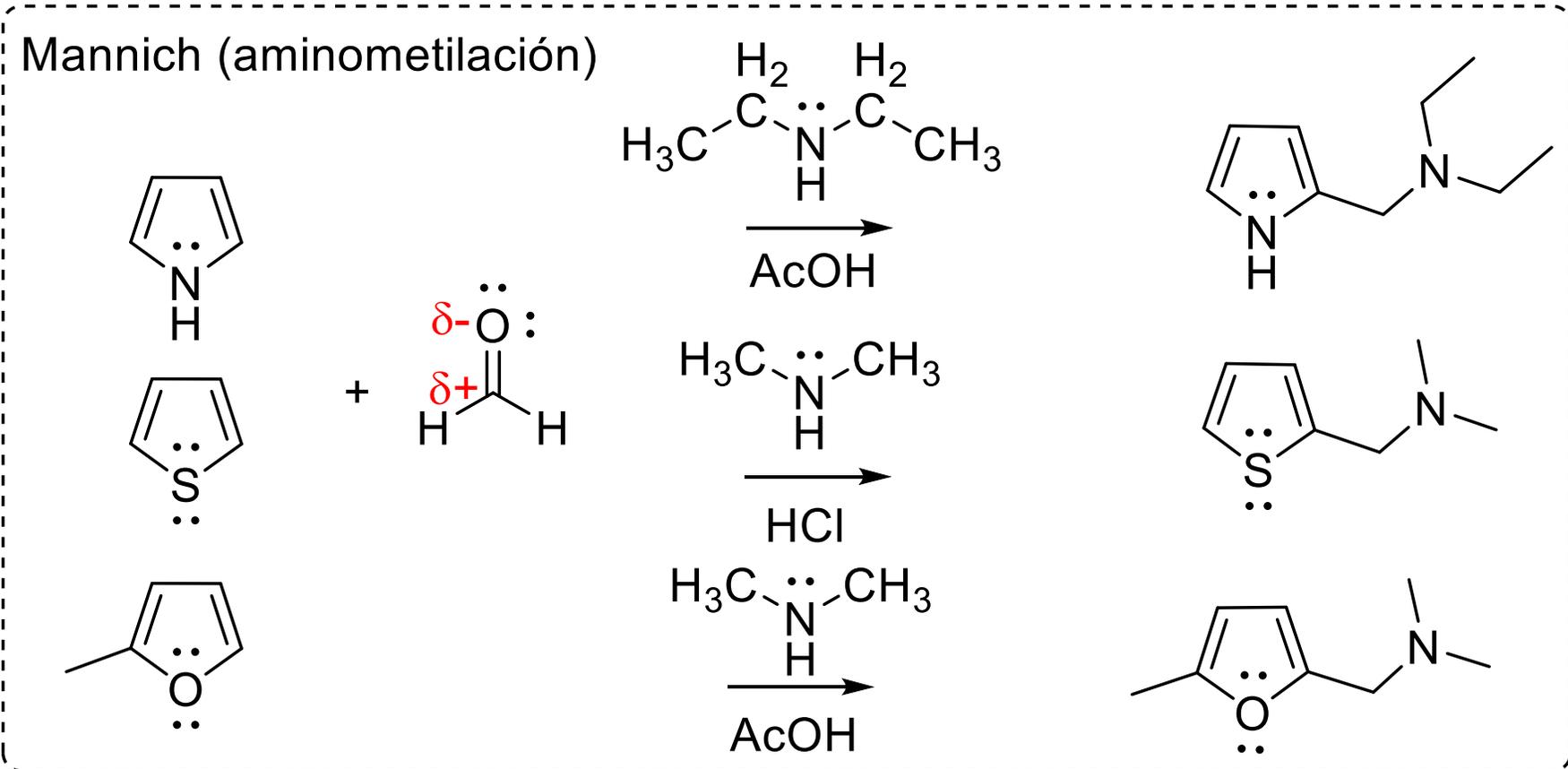
4.



5.

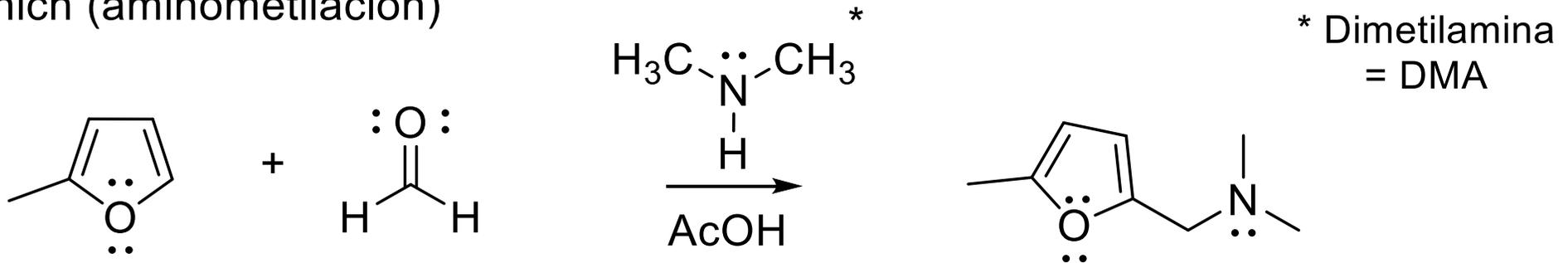


# Reacción de Mannich

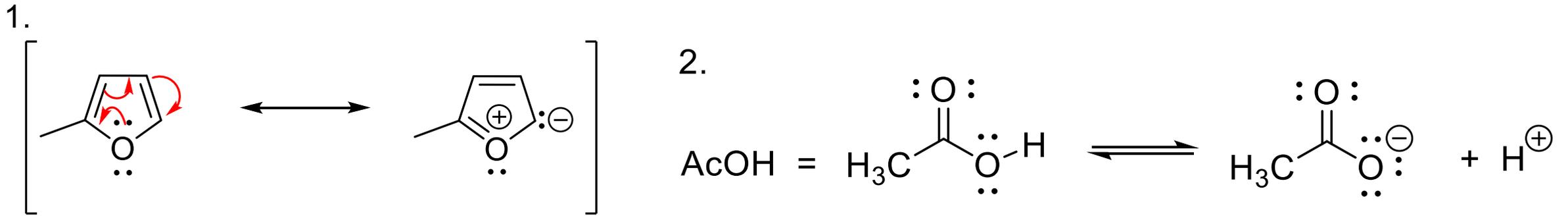


# Reacción de Mannich-mecanismo

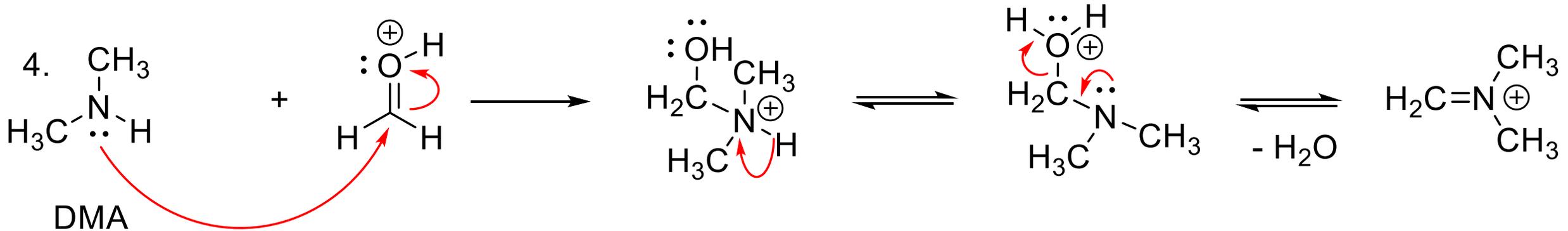
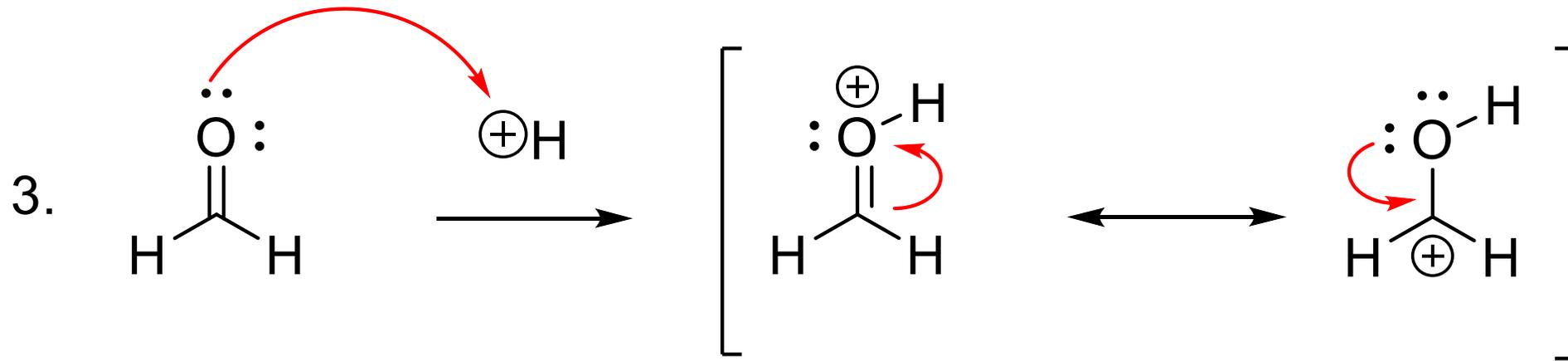
Mannich (aminometilación)



Mecanismo por partes

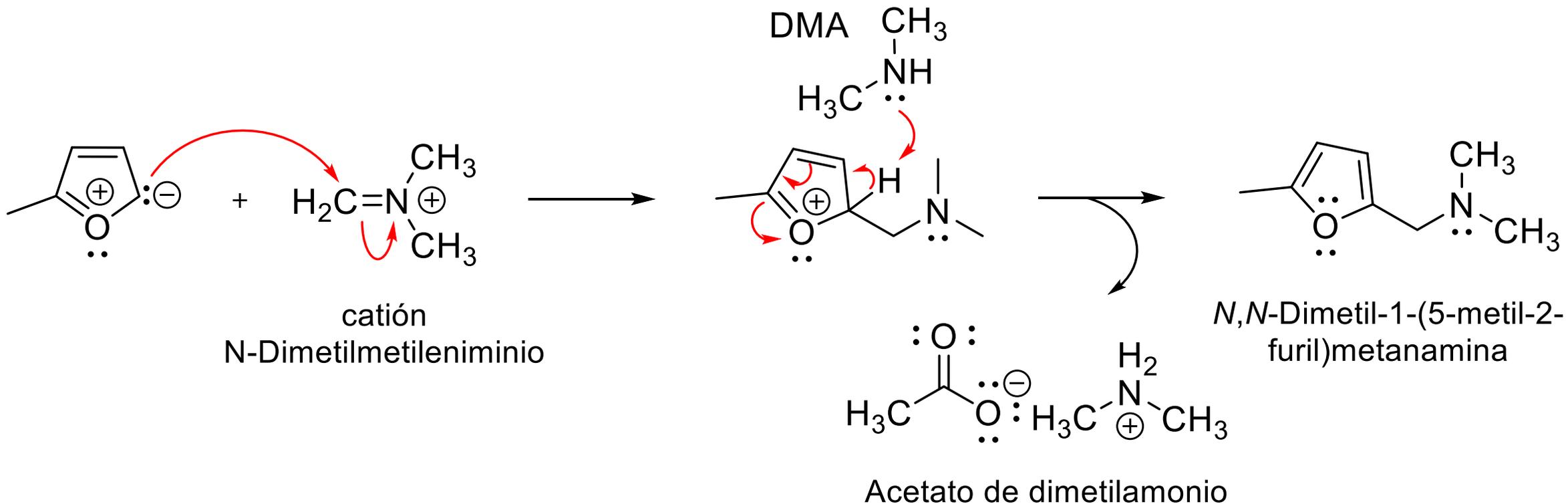


# Reacción de Mannich-mecanismo



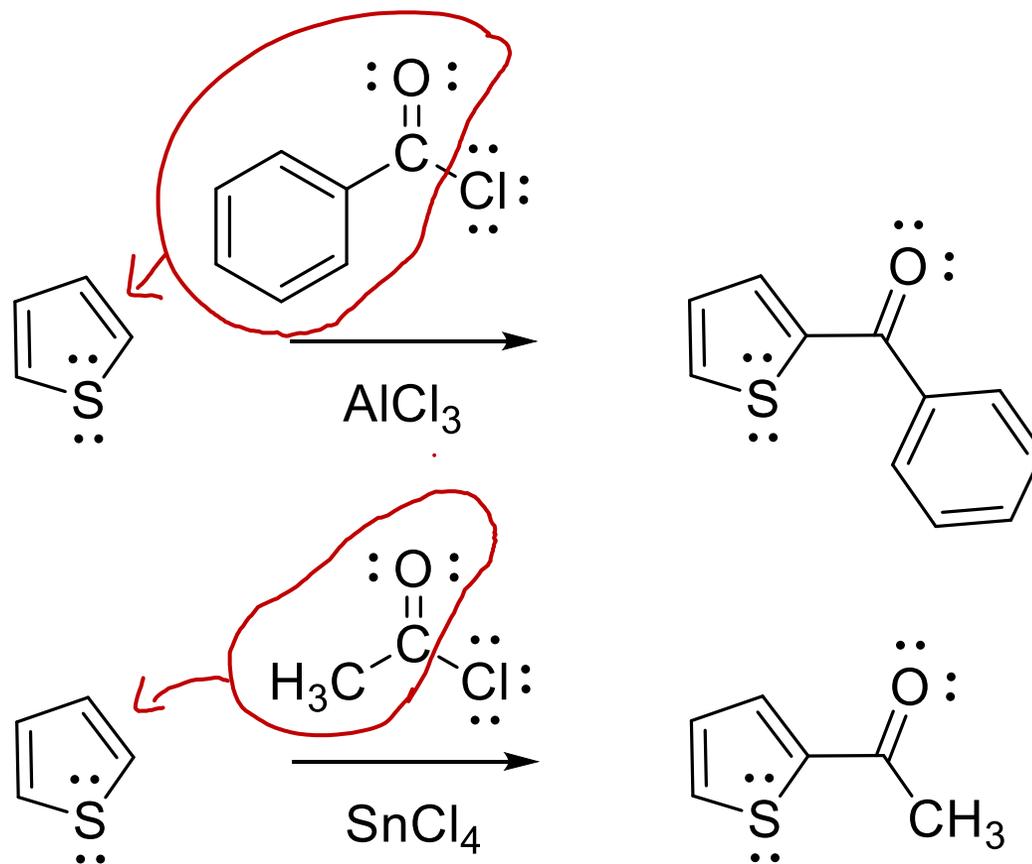
# Etapa de amino-metilación

5.

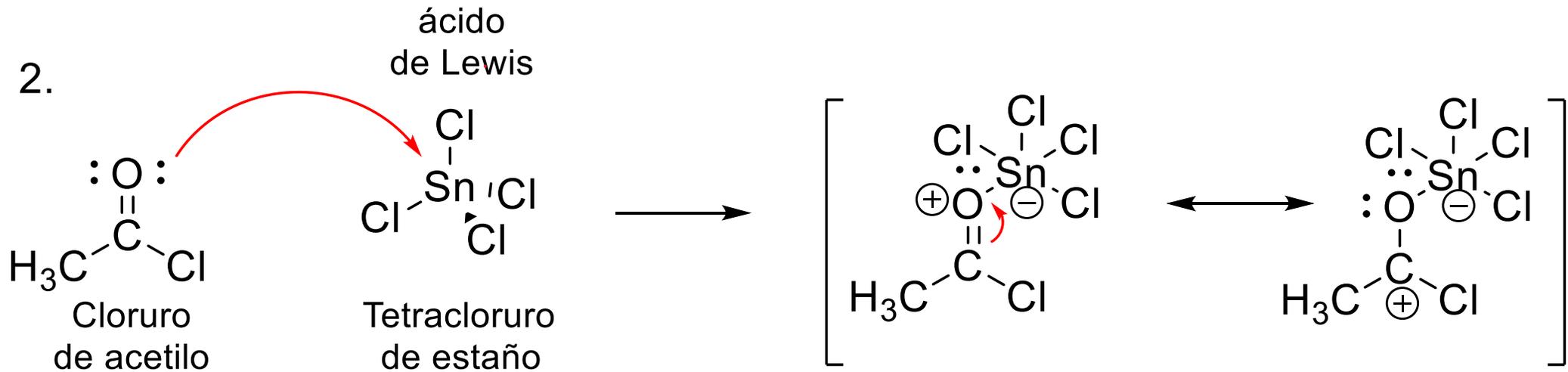
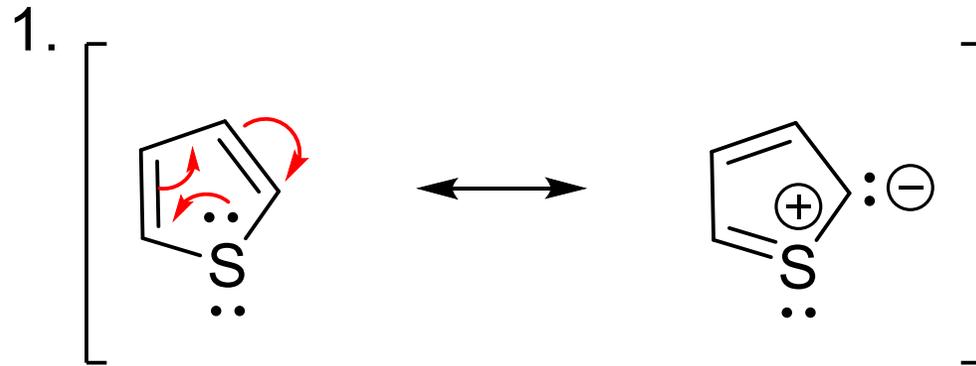


# Tiofeno: Algunas propiedades químicas particulares

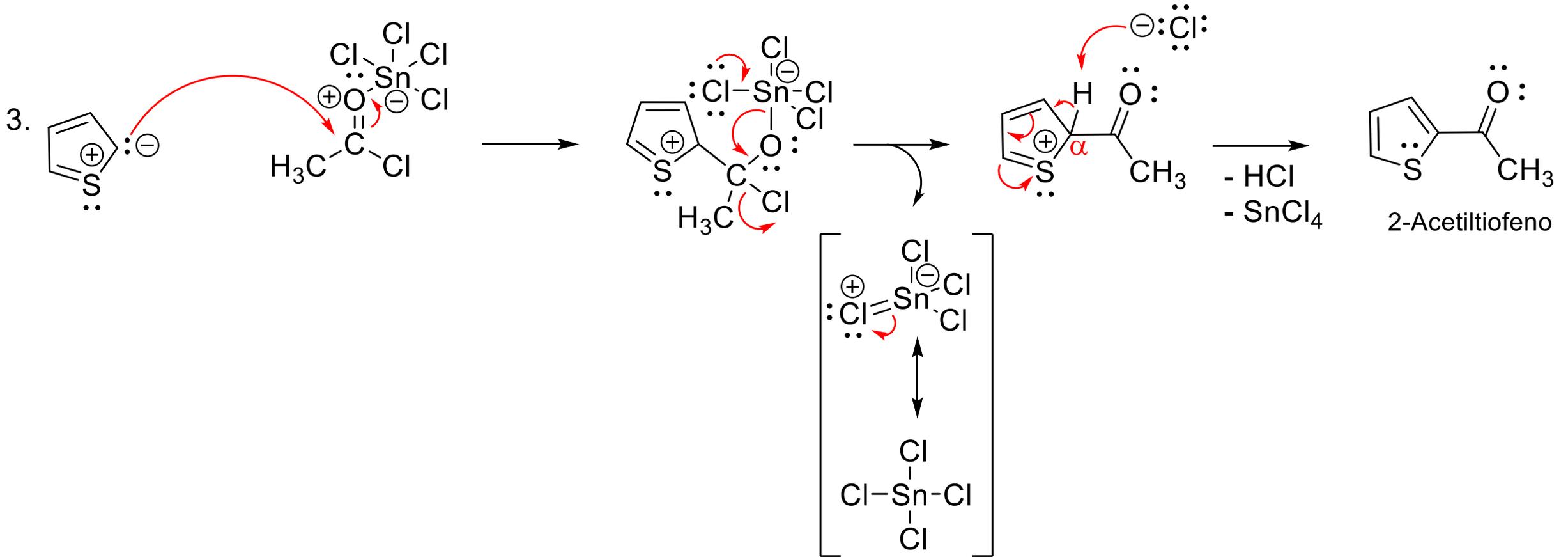
Mientras que el pirrol y el furano son poco estables frente a los ácidos de Lewis de la acilación y alquilación de Friedel-Crafts, los tiofenos, debido a su mayor carácter aromático, favorecen más este tipo de reacciones.



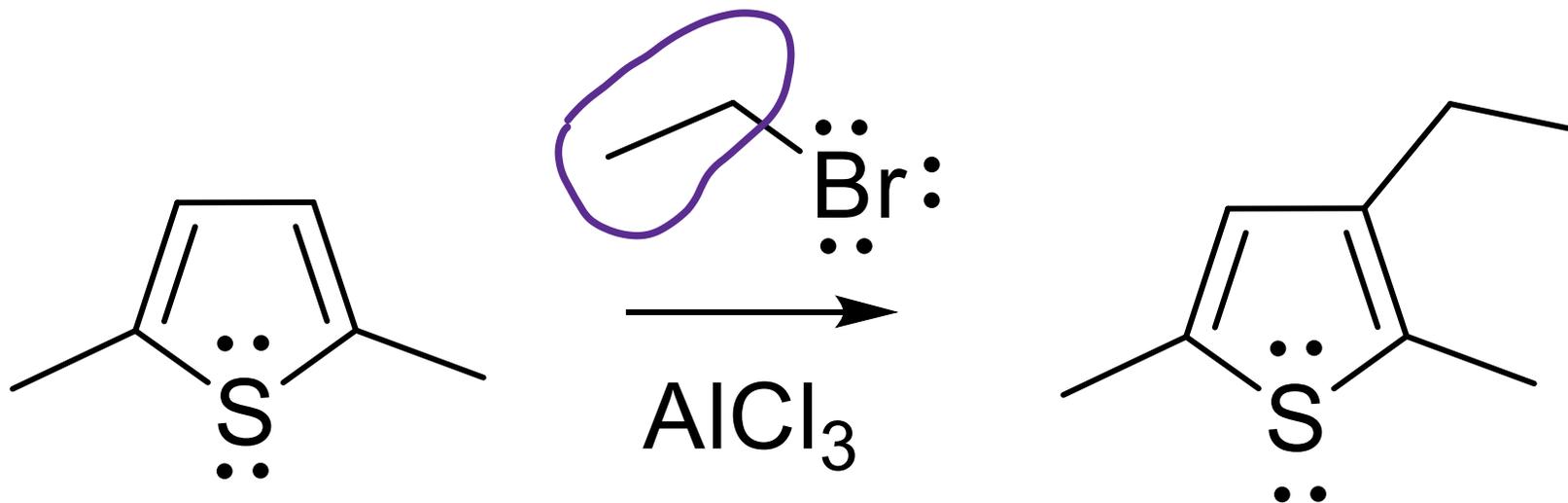
# Acilación: mecanismo por partes



# Acilación

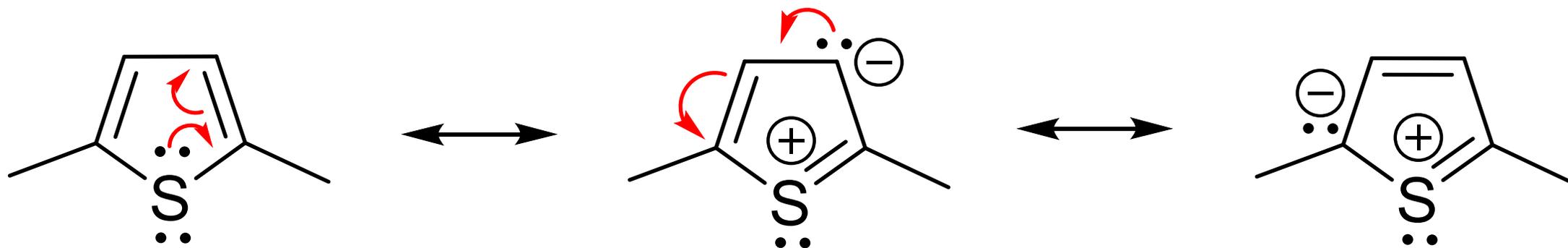


# Alquilación de Friedel-Crafts

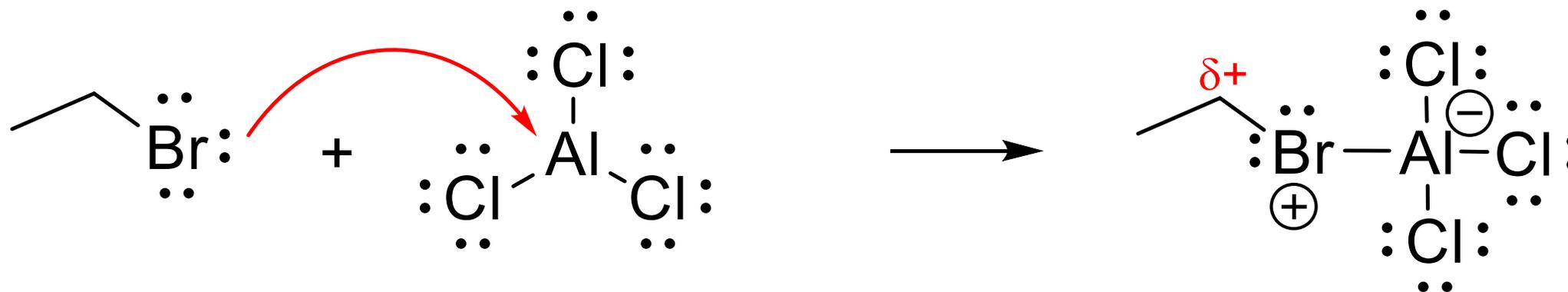


# Mecanismo por partes

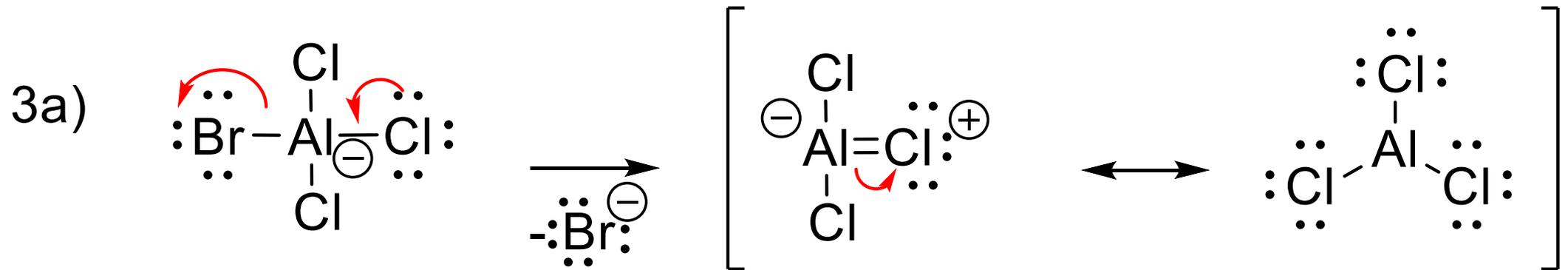
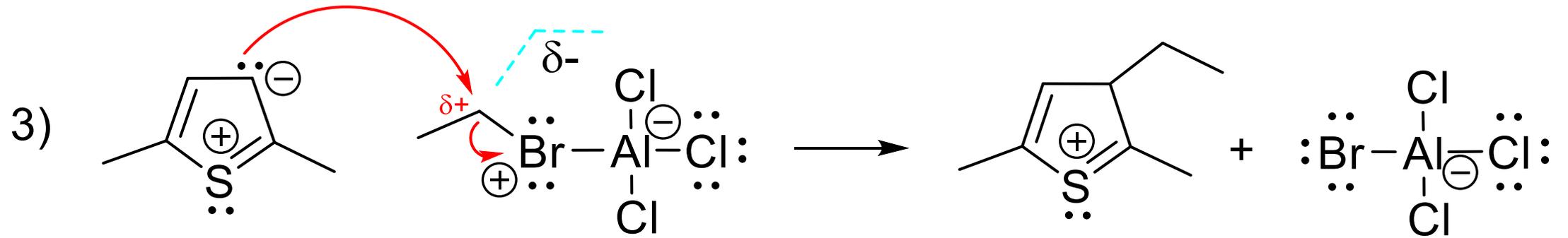
1)



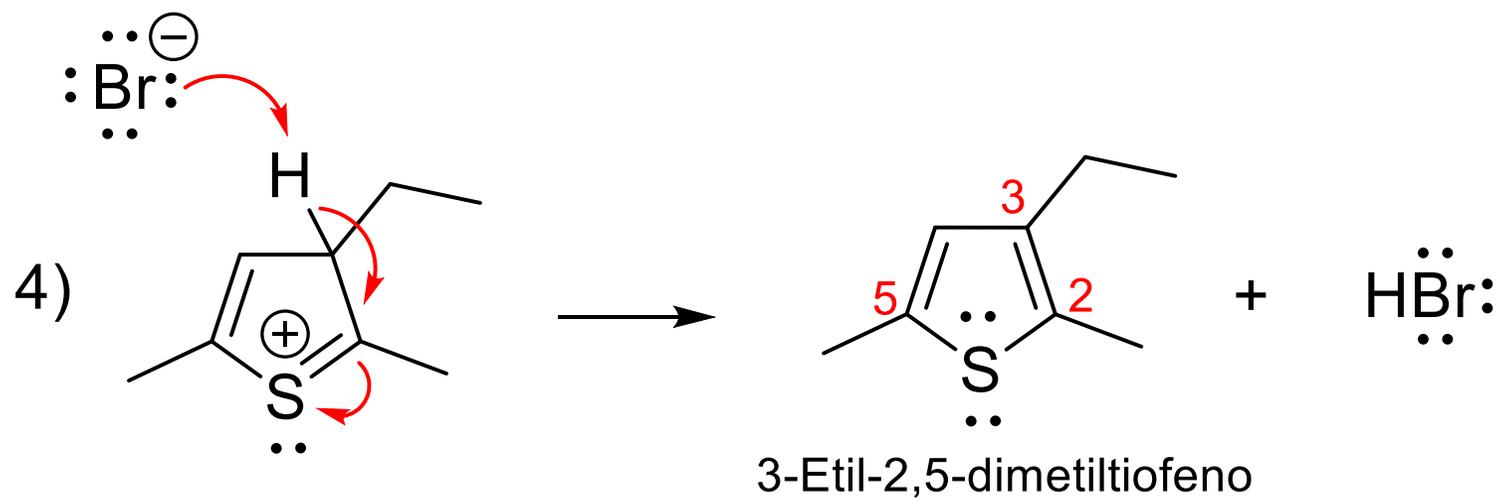
2)



# Mecanismo por partes

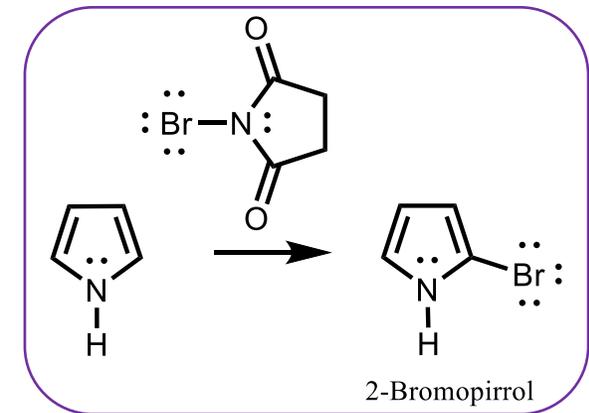
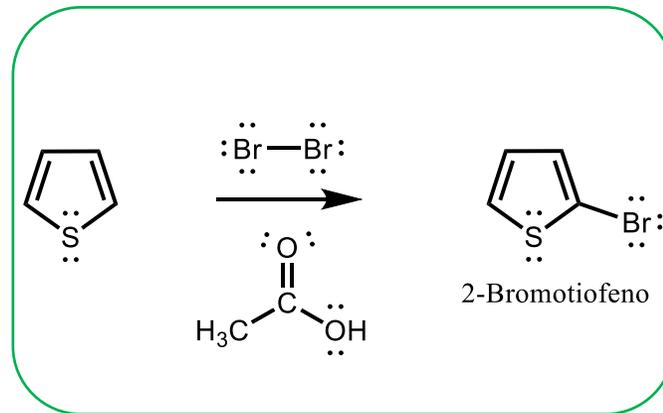
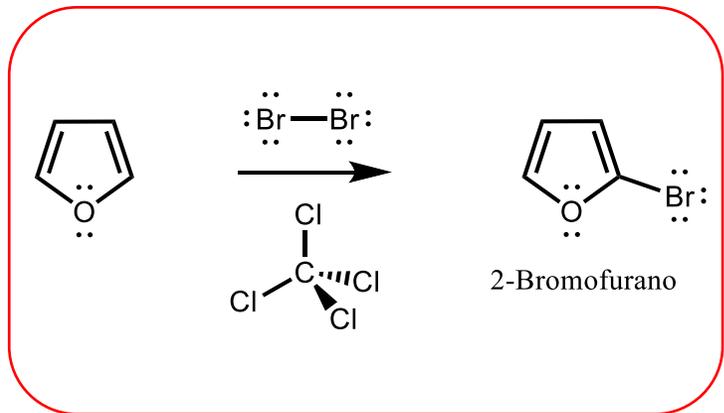


# Mecanismo de alquilación de Friedel-Crafts

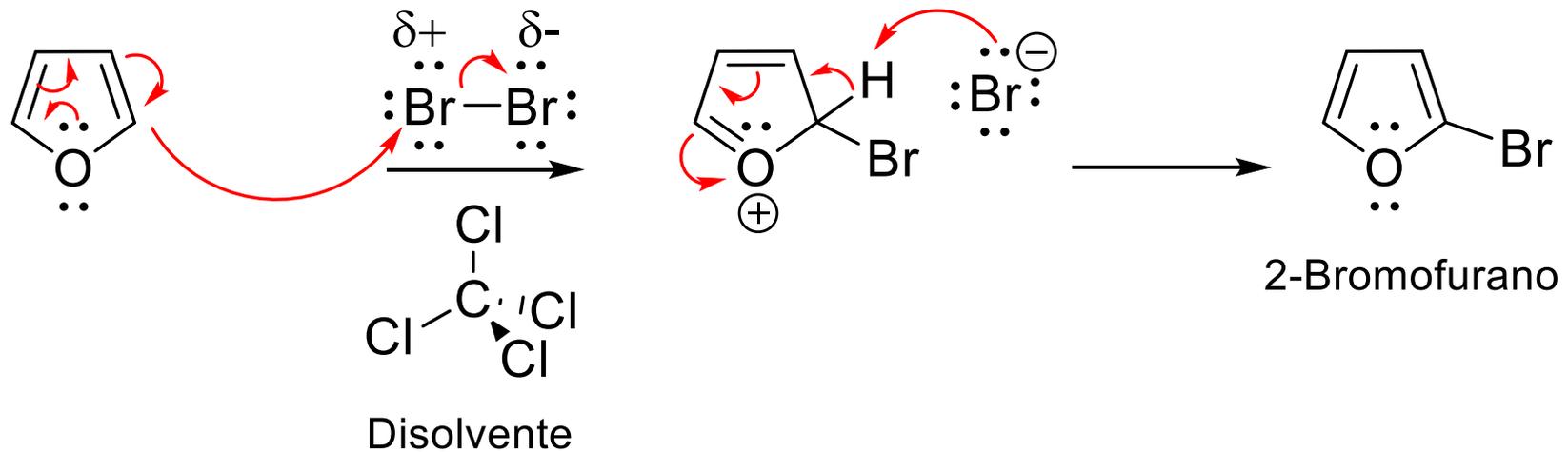
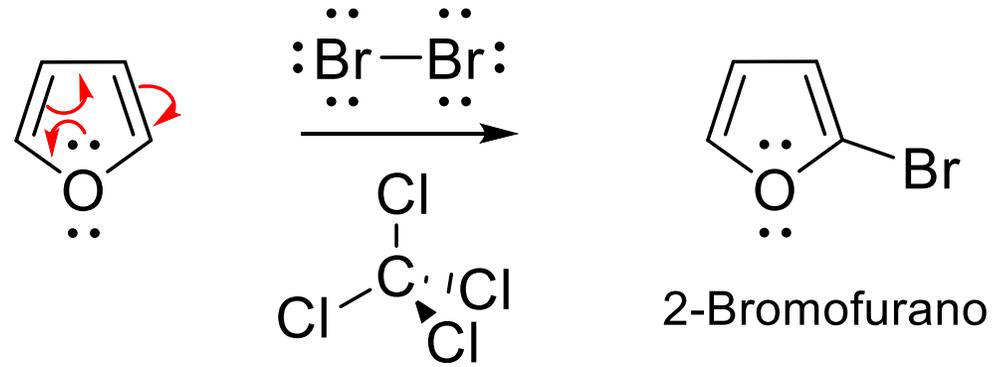


# Halogenación

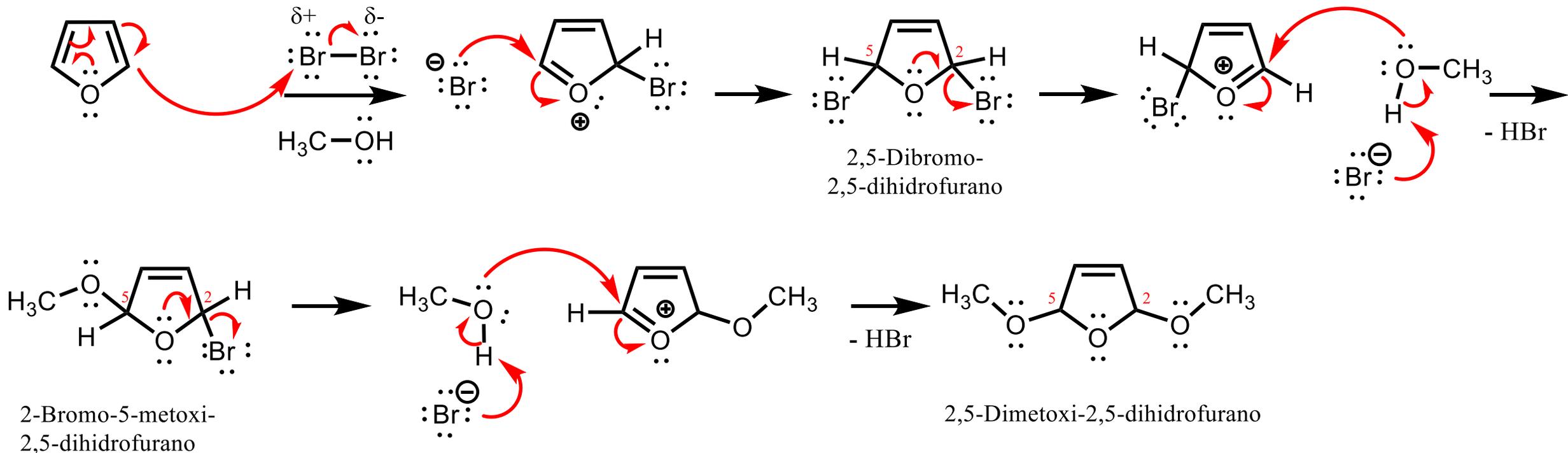
- La halogenación del furano es difícil de controlar, ya que, por su alta reactividad, produce polihalogenados, pero la bromación en  $\text{CCl}_4$  genera 2-bromofurano. La bromación en  $\text{AcOH}$  de tiofeno rinde 2-bromotiofeno, y la de pirrol con N-bromosuccinimida, 2-bromopirrol.



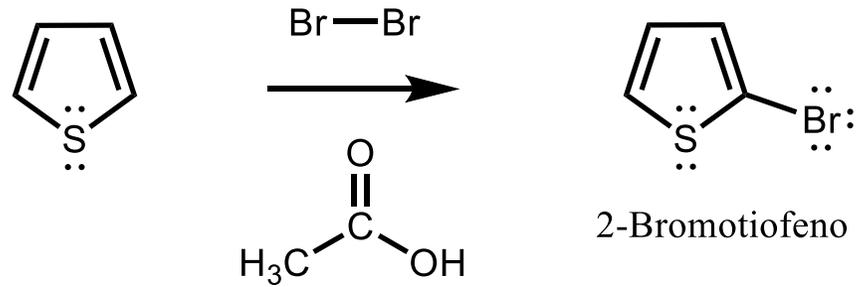
# Bromación de furano



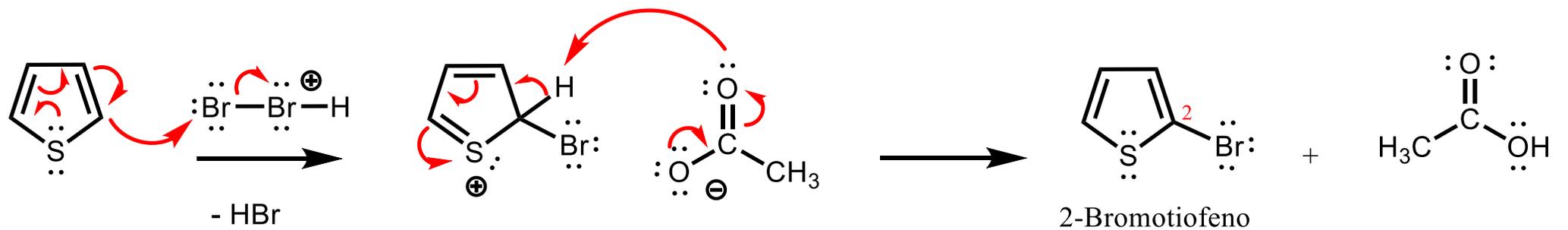
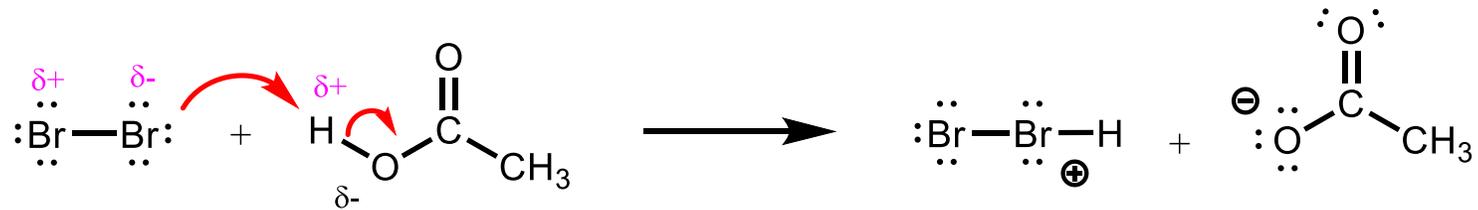
La bromación de furano en presencia de MeOH genera un producto dimetoxilado de adición, no de sustitución



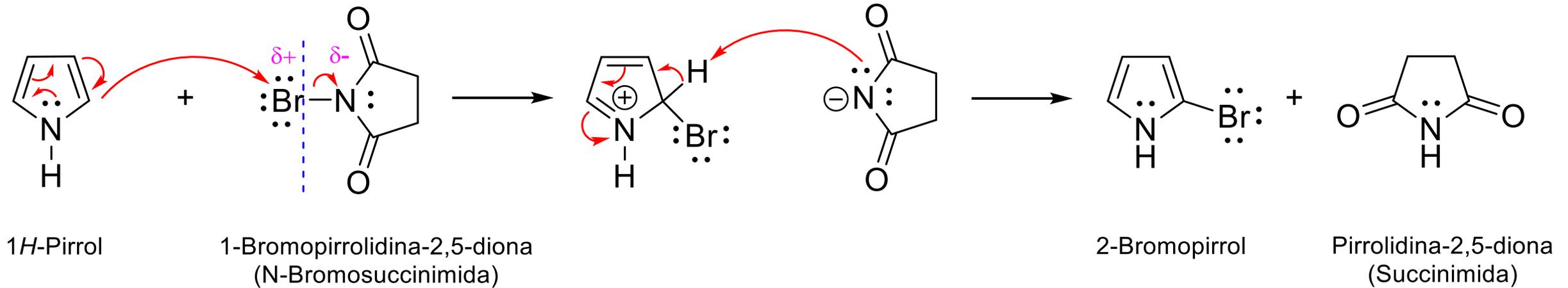
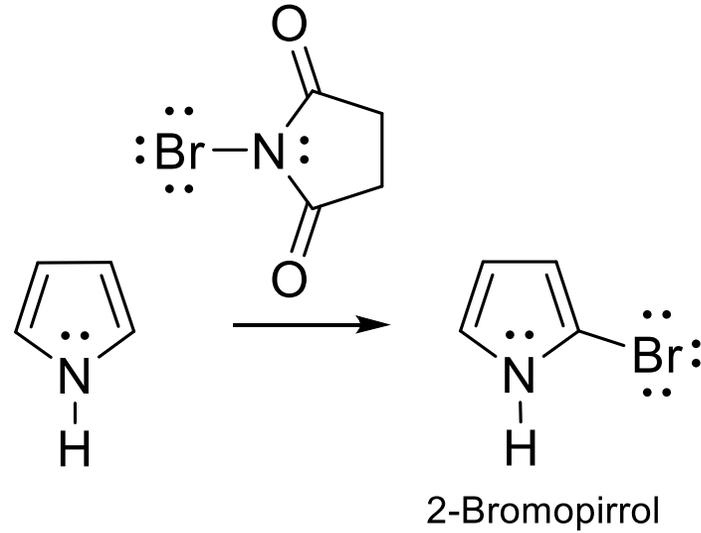
# Bromación de tiofeno



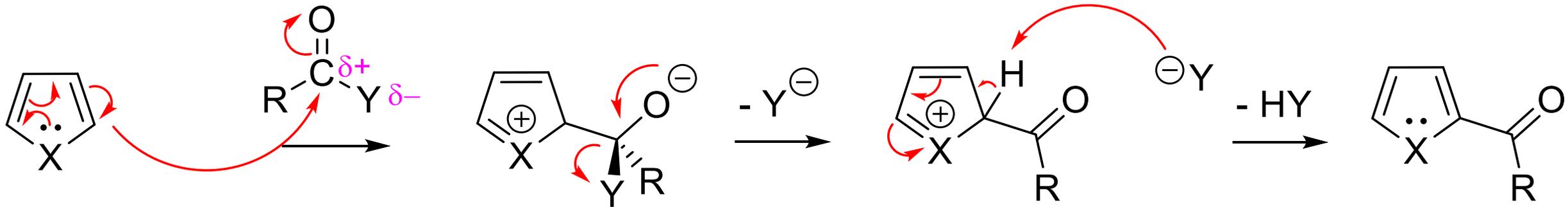
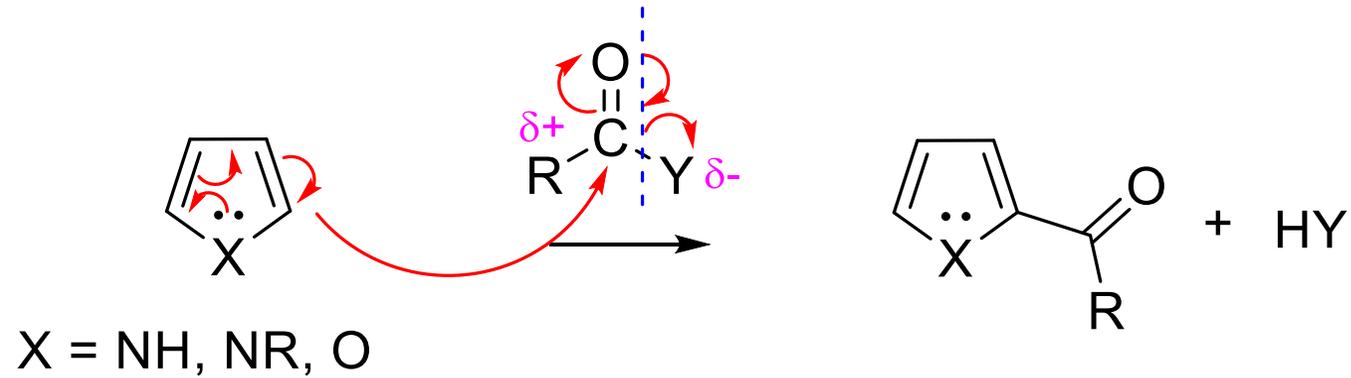
Dos etapas:



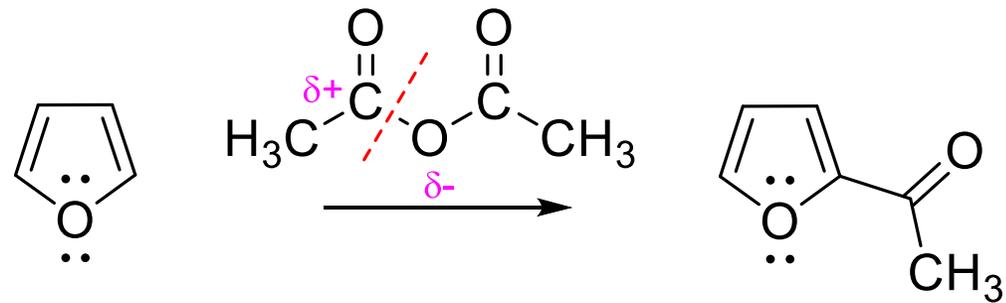
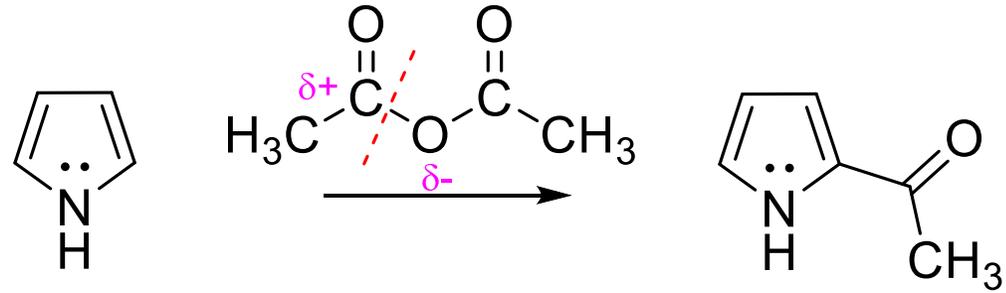
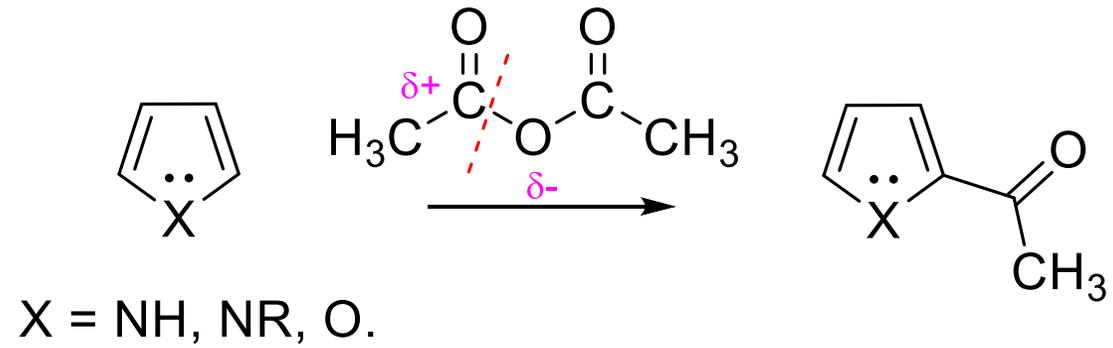
# Bromación de pirrol



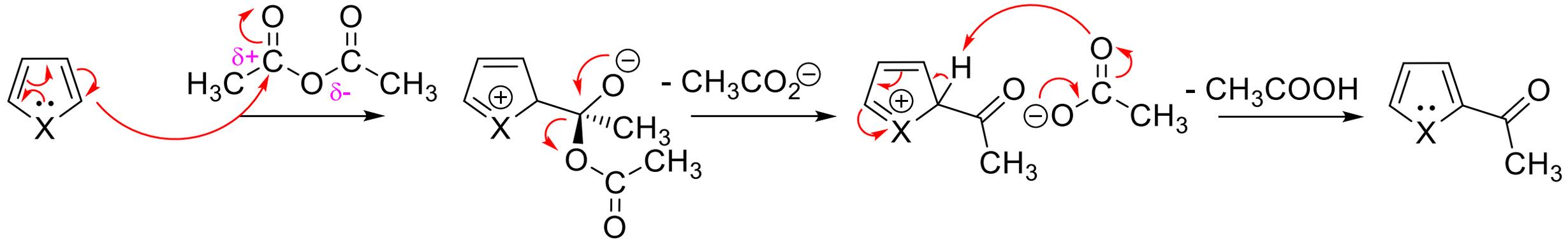
# Acilación de pirrol y furano



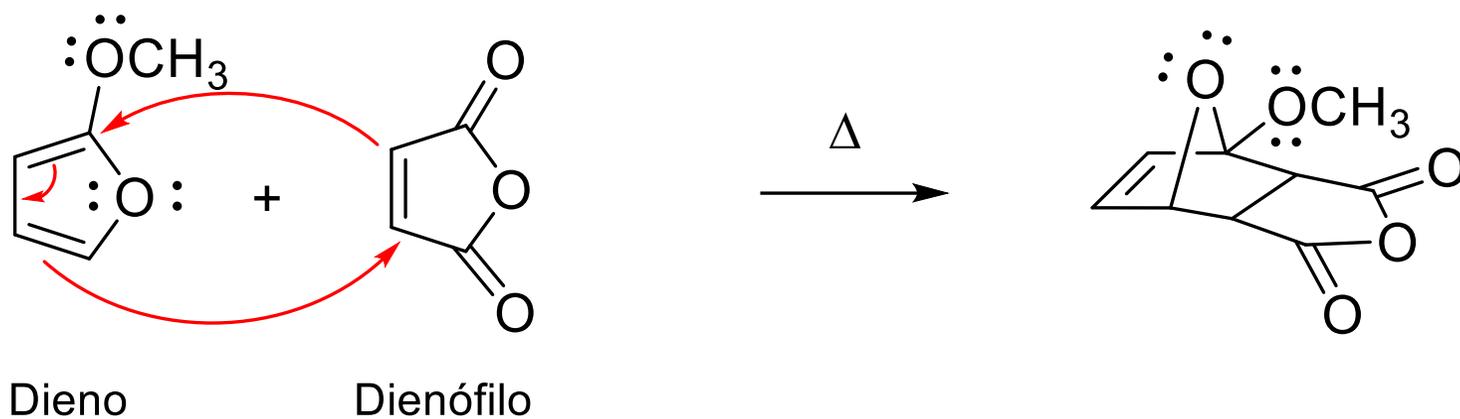
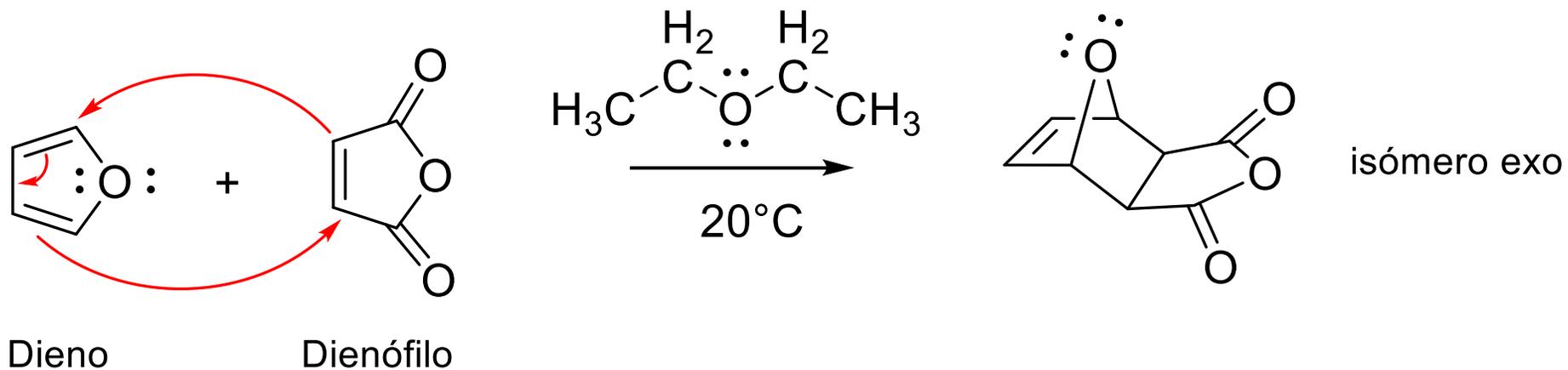
# Acilación: Acetilación



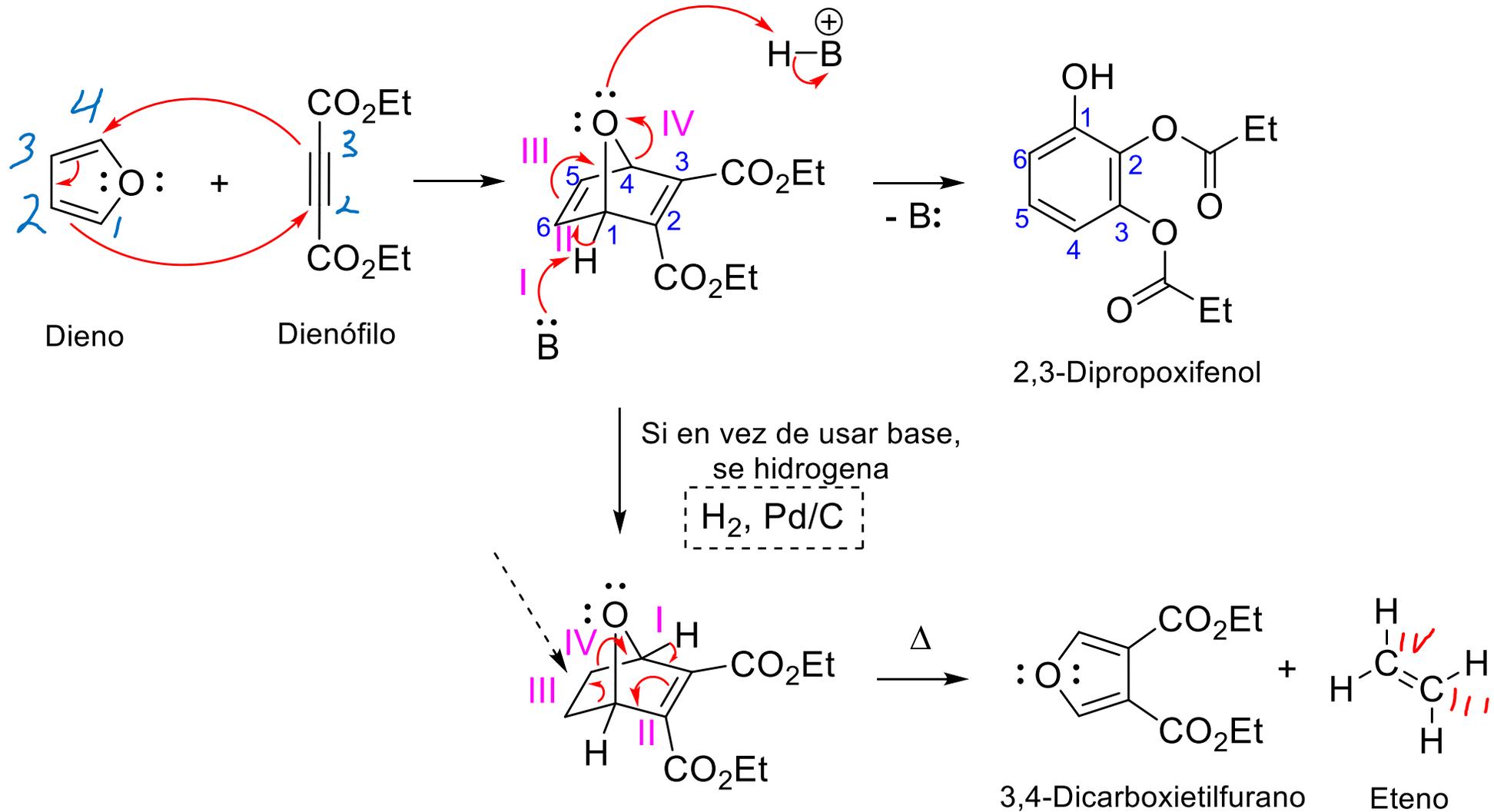
# Mecanismo de acetilación



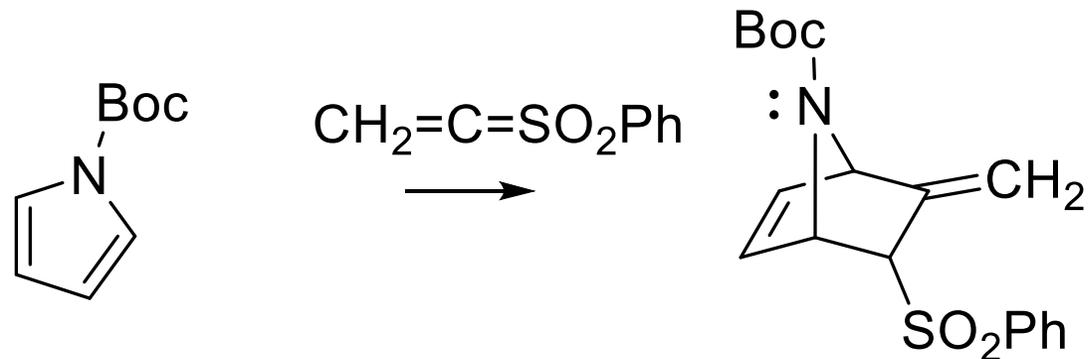
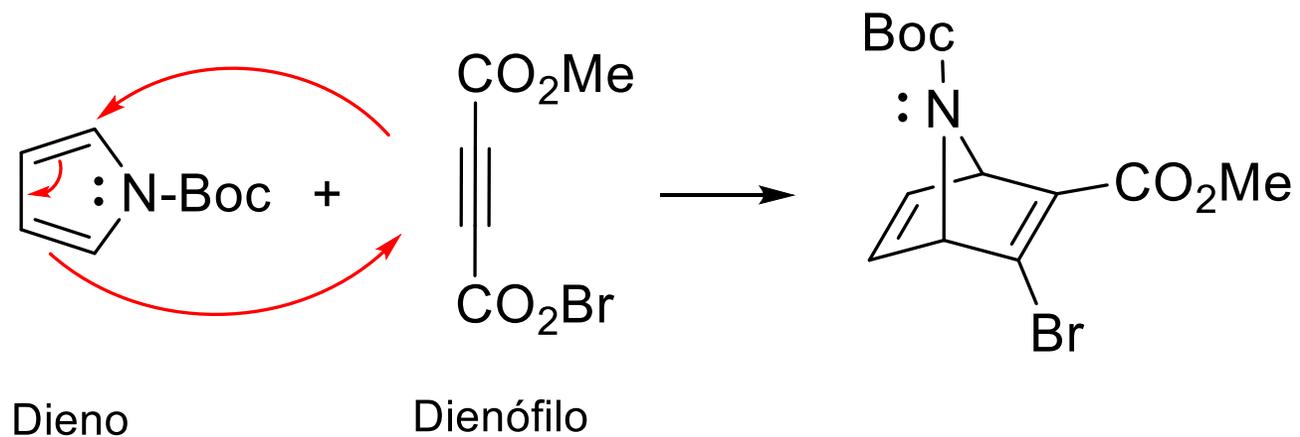
# Furano: reacciones como dieno



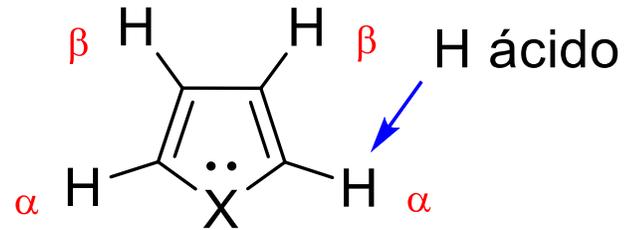
# Furano: reacciones como dieno



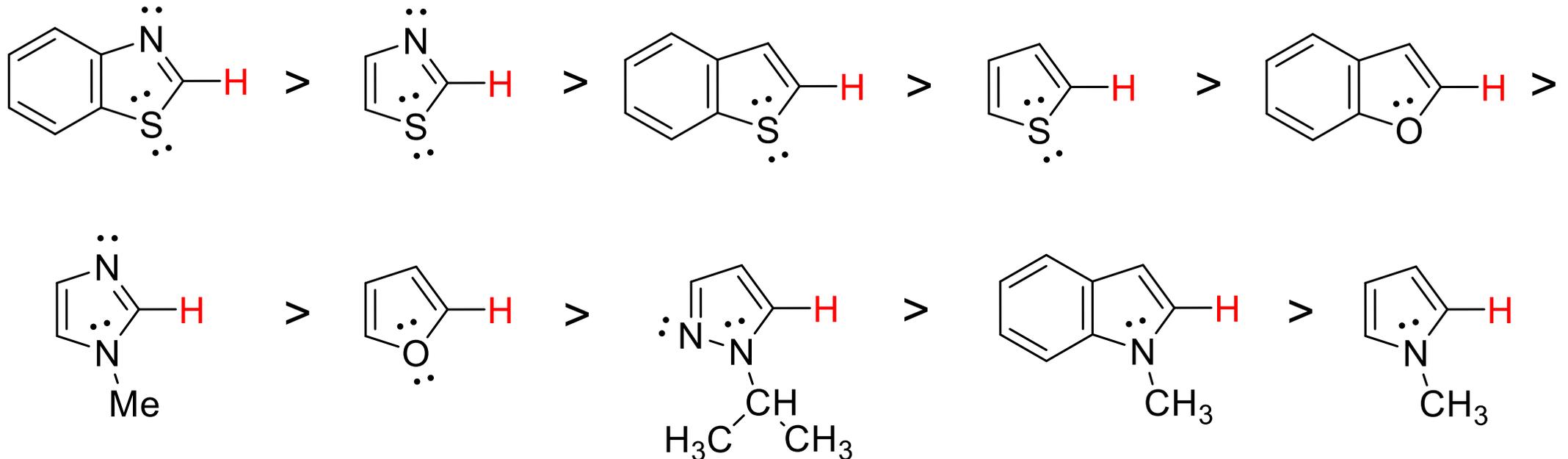
# NR-Pirrol: reacciones como dieno



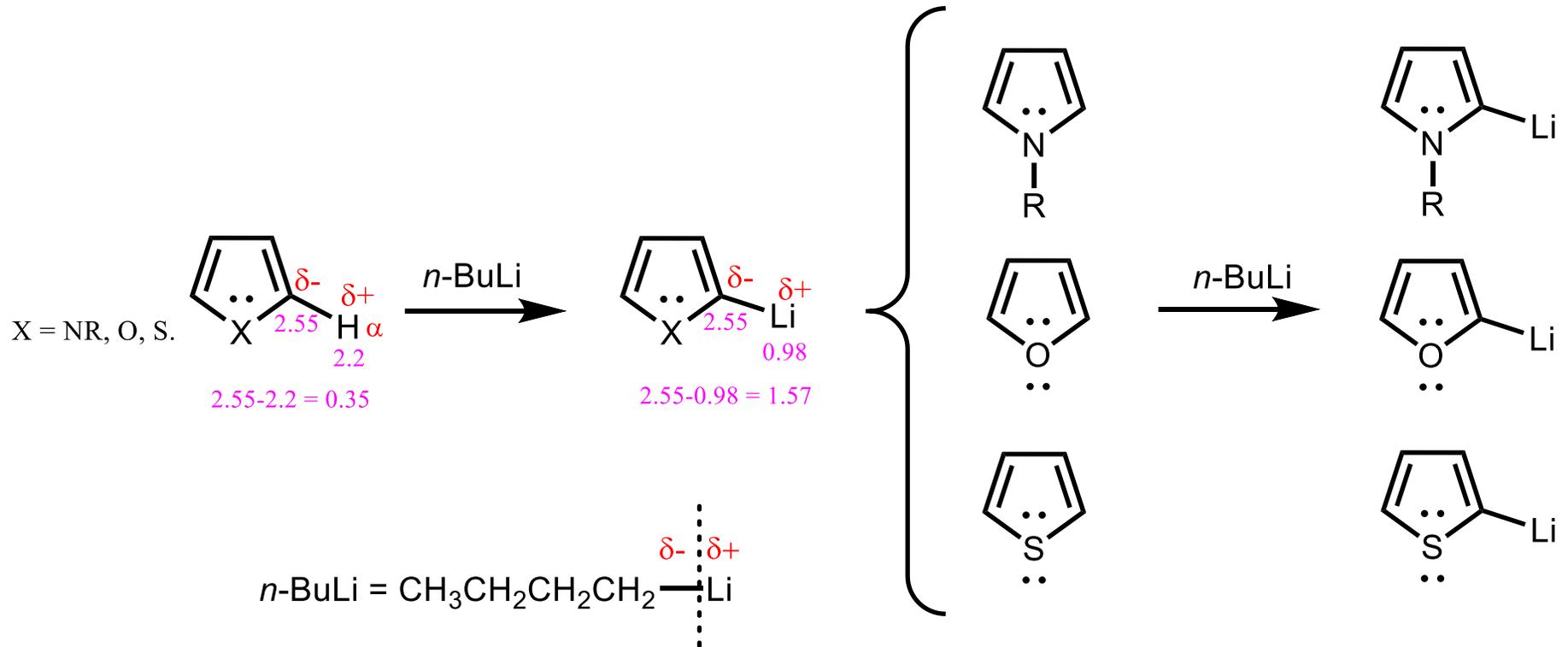
# Acidez de los H $\alpha$ en heterociclos de 5 átomos



Disminuye la acidez (aumenta  $pK_a$ ) del C e H $\alpha$



# Metalación: Es una reacción de SEA

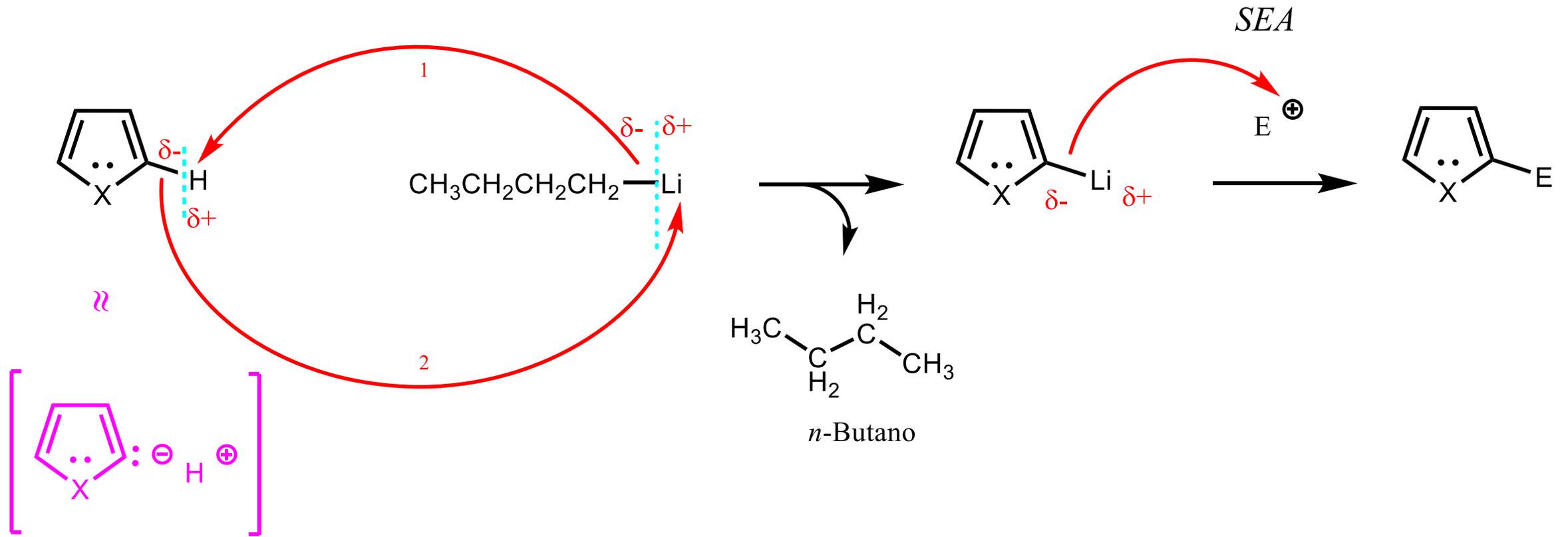


$\delta$  = Carga parcial  
 Electronegatividad

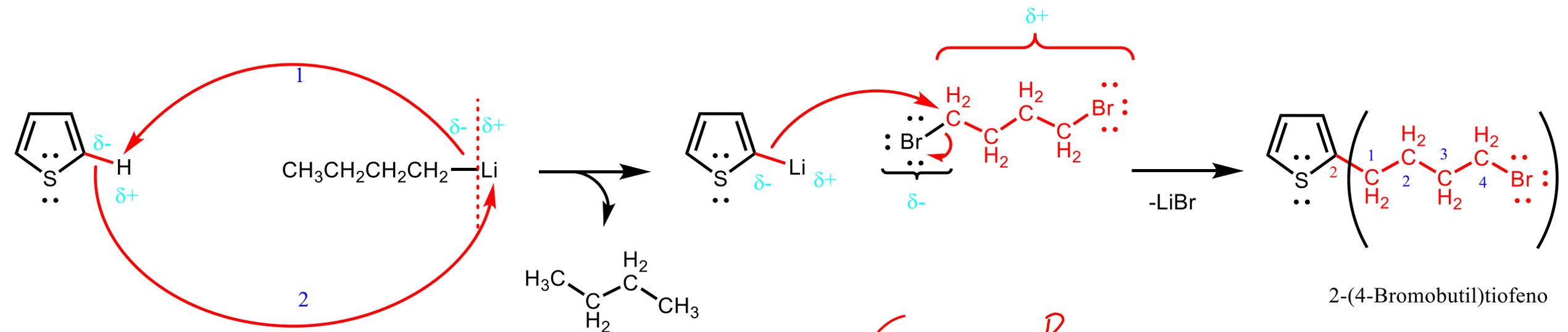
Diferencia de electronegatividades  
y carácter del enlace

> 1.9 Iónico  
 < 1.9 Covalente

# Mecanismo

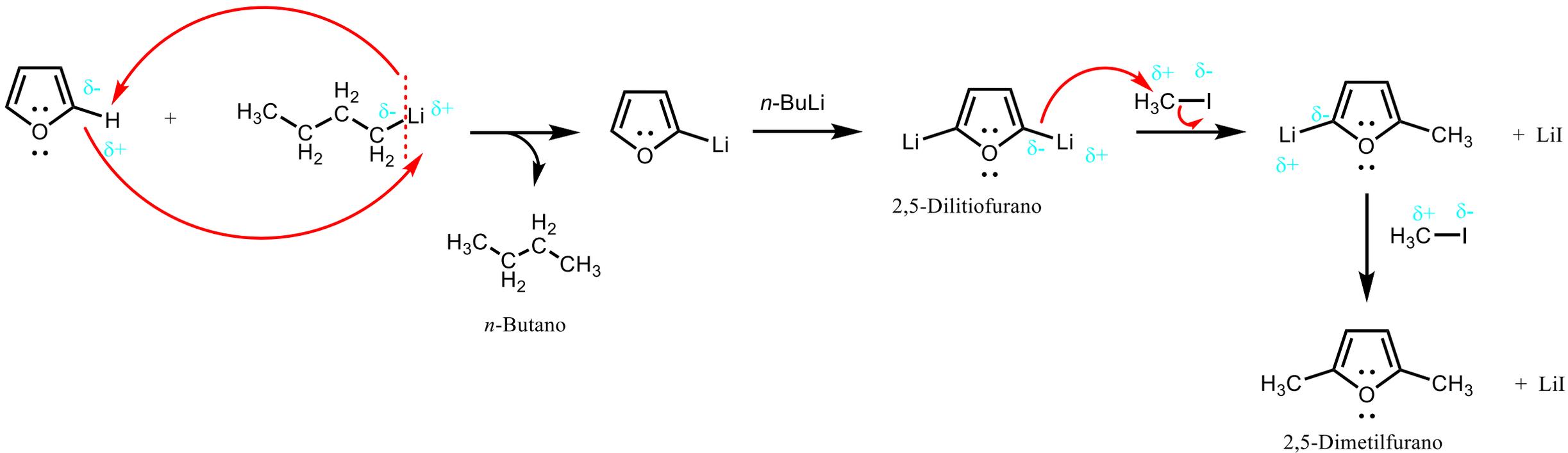


# Metalación para tiofeno

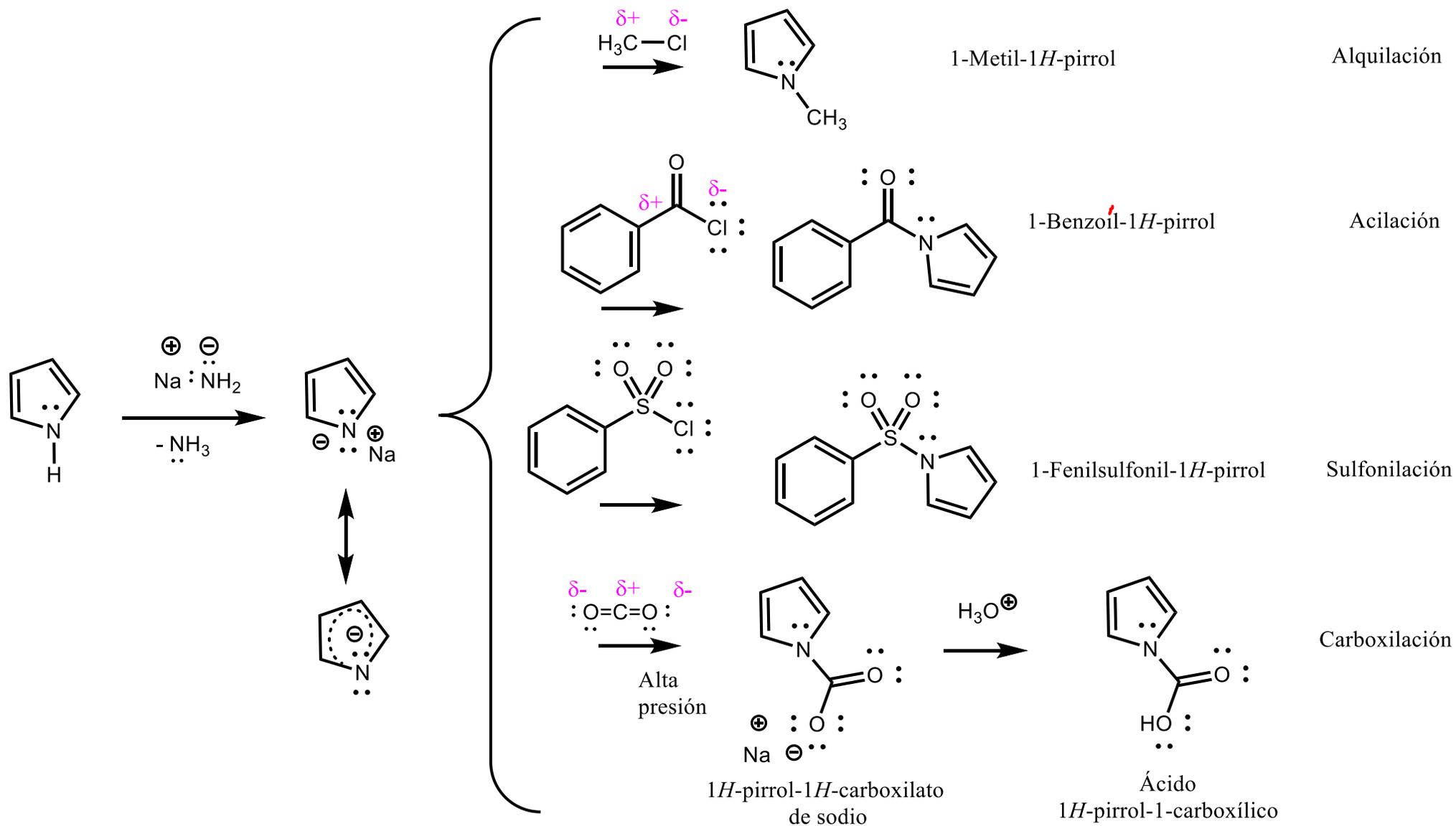


$\text{C}_{255}, \text{Br}_{268}$   
 $\approx 0.3$

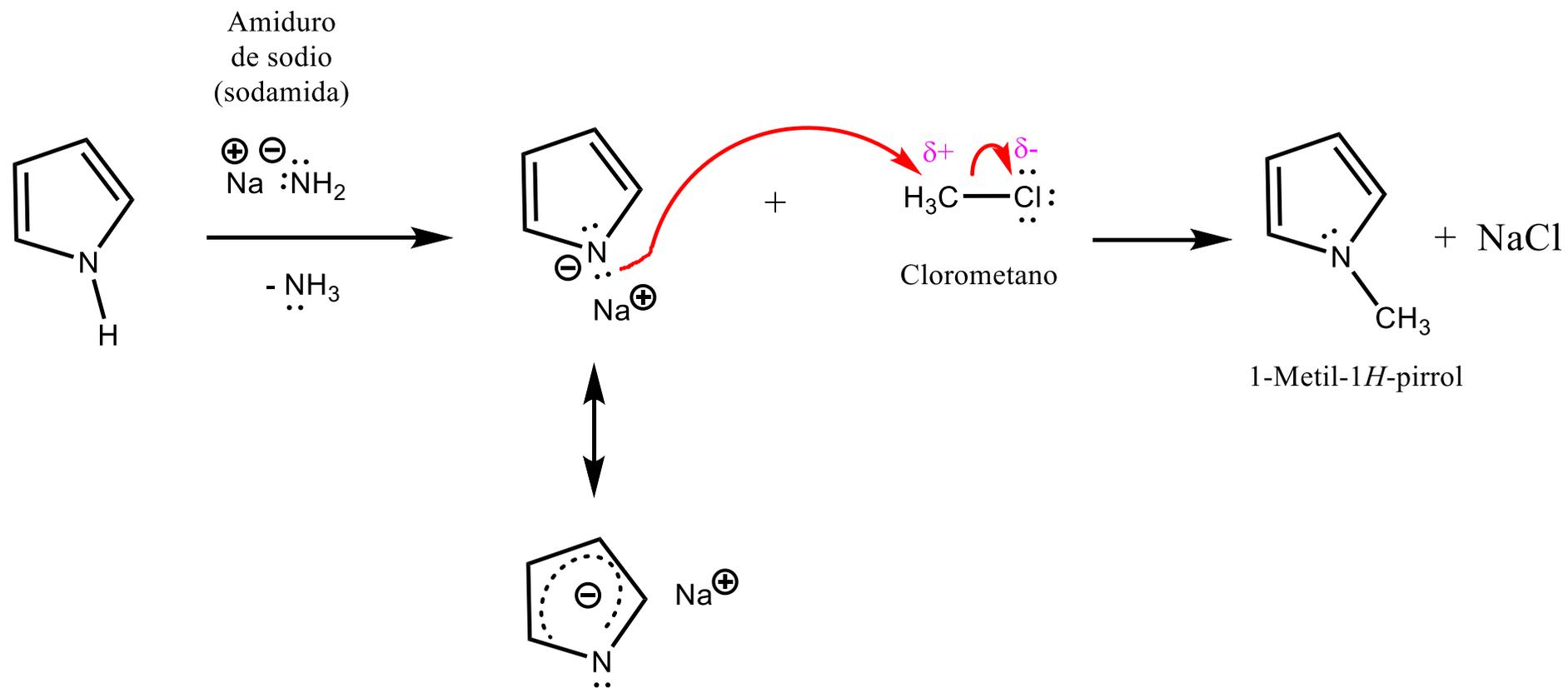
# Metalación para furano



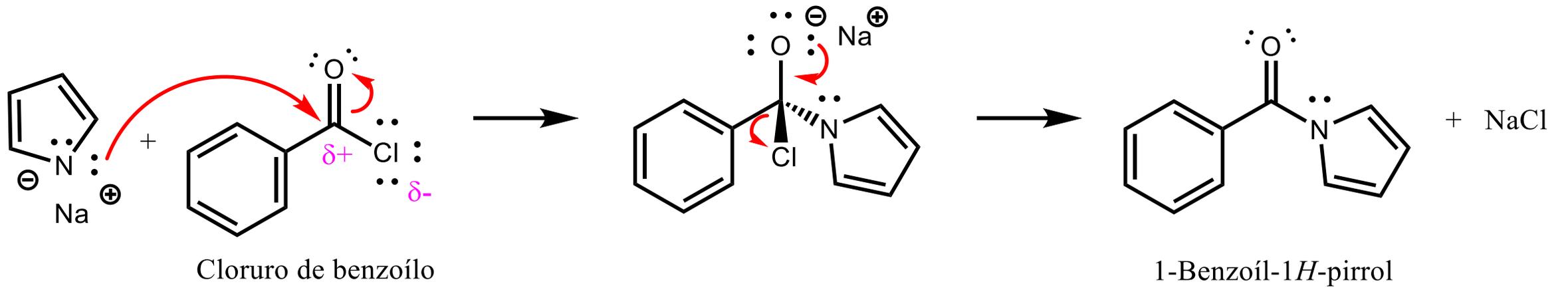
# Sustracción del *H1* del 1*H*-pirrol y reacciones de su anión



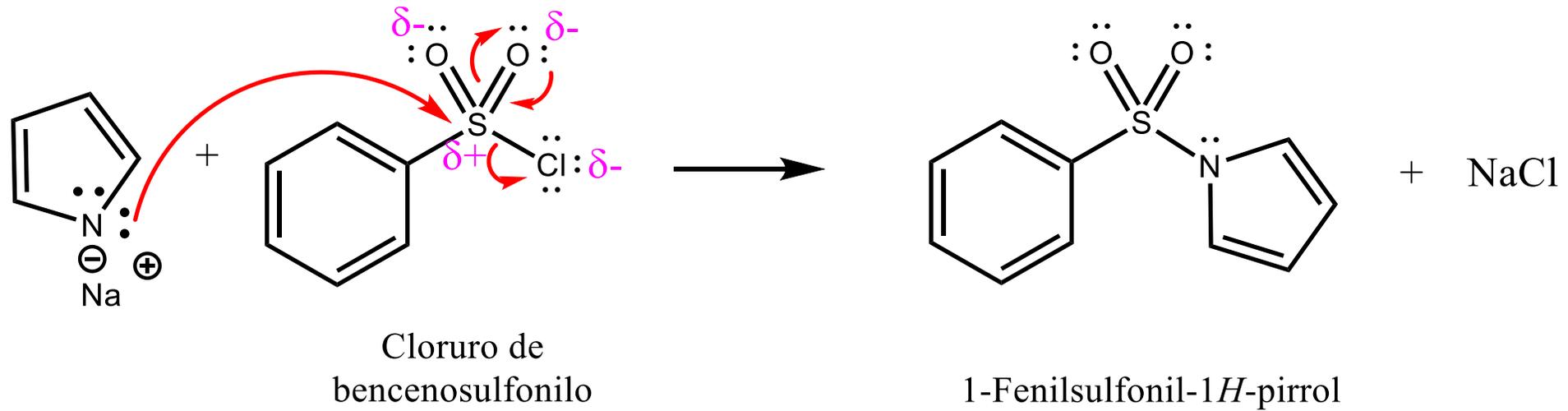
# Alquilación



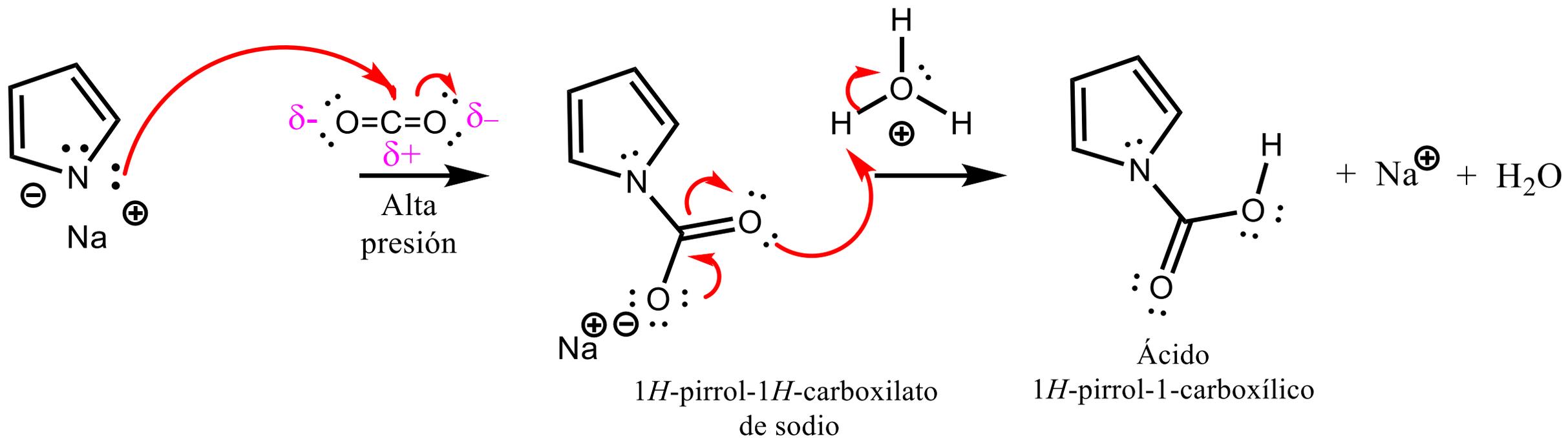
# Acilación



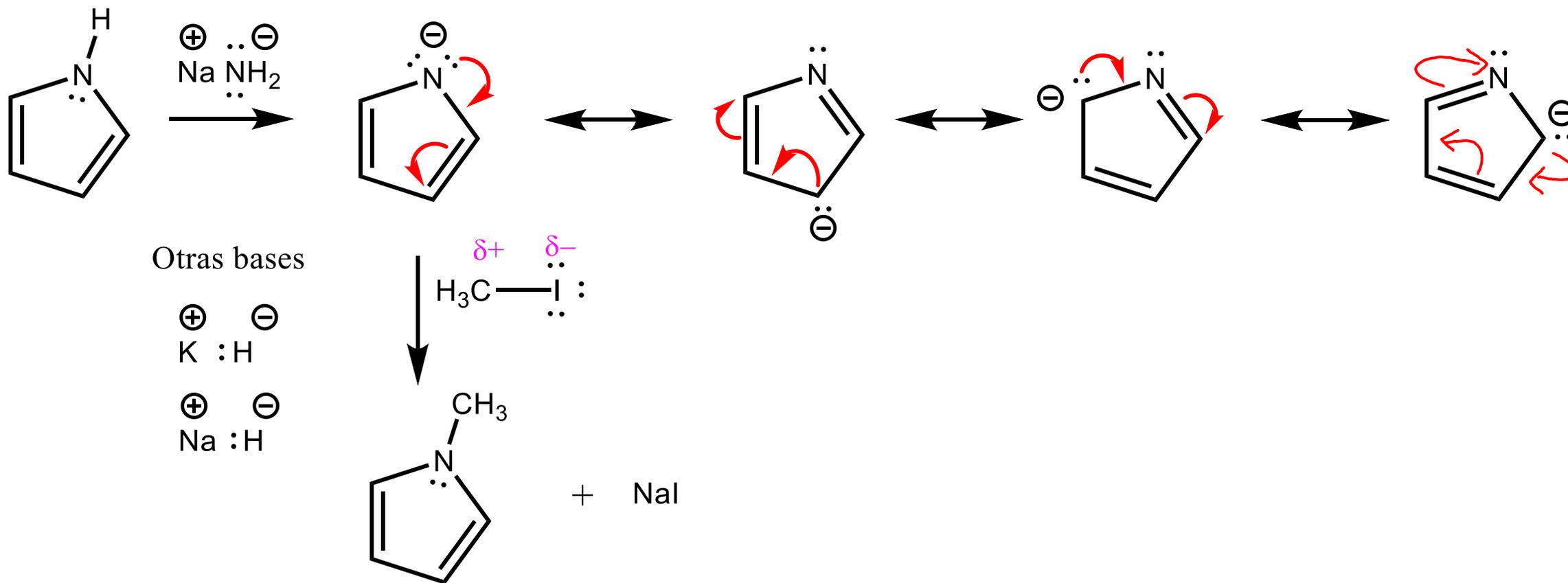
# Sulfonilación



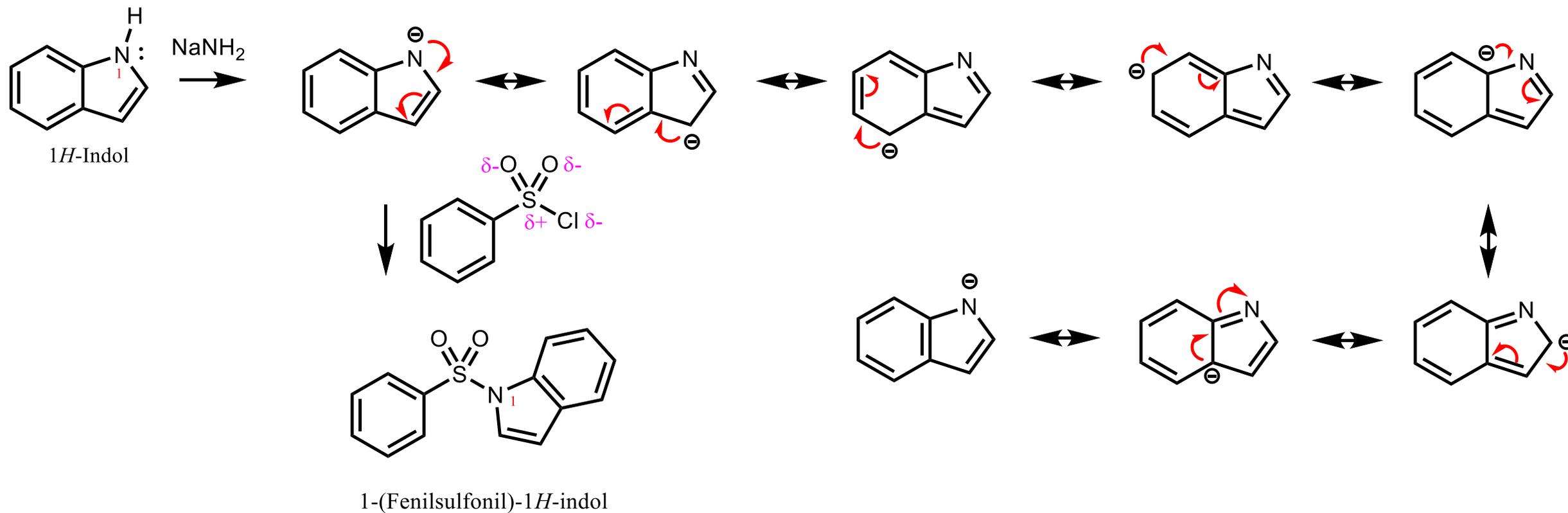
# Carboxilación



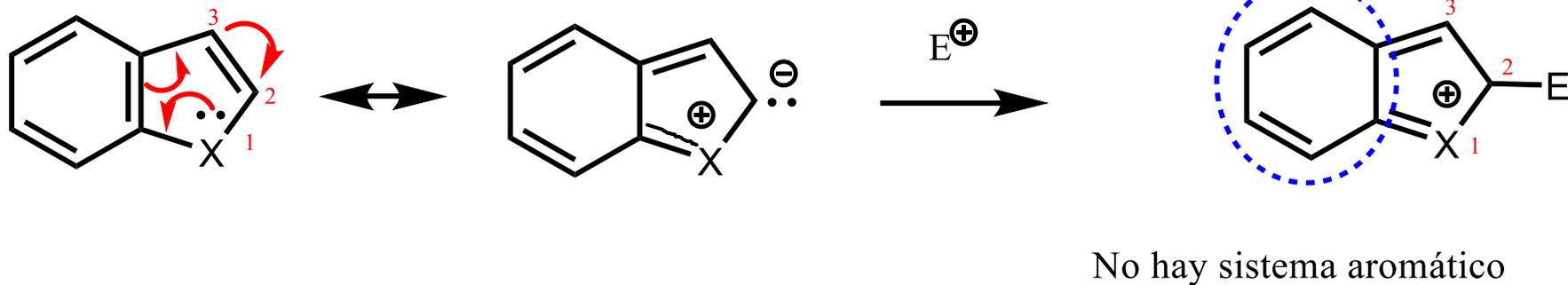
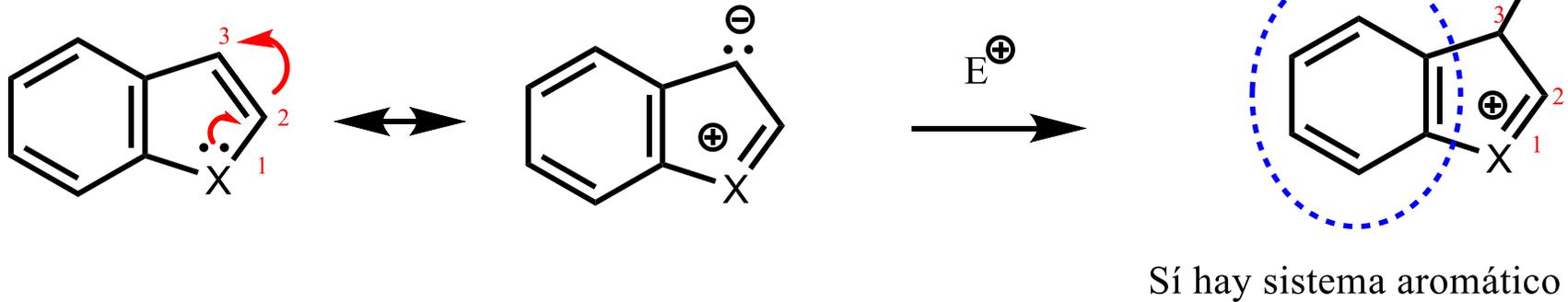
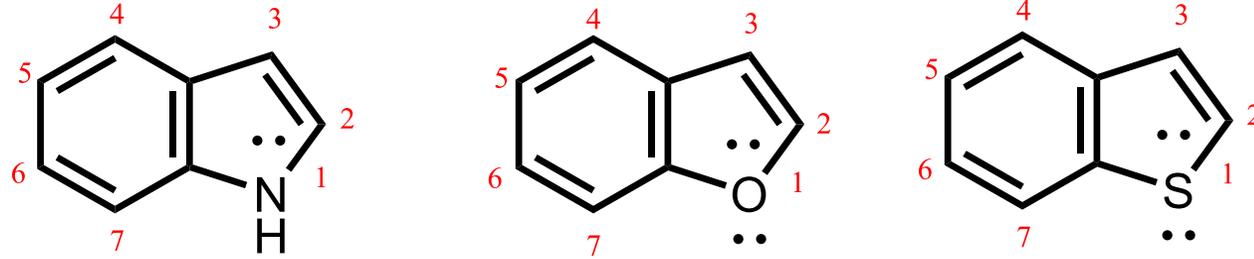
# Ejemplo: Formación de N-anión y alquilación



# Formación de anión del 1*H*-indol

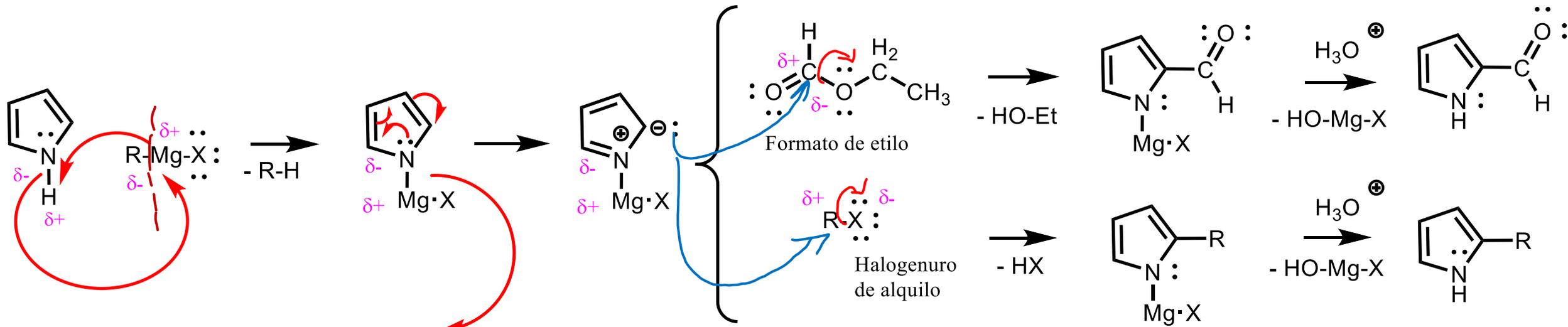


# SEA y resonancia en los derivados fusionados



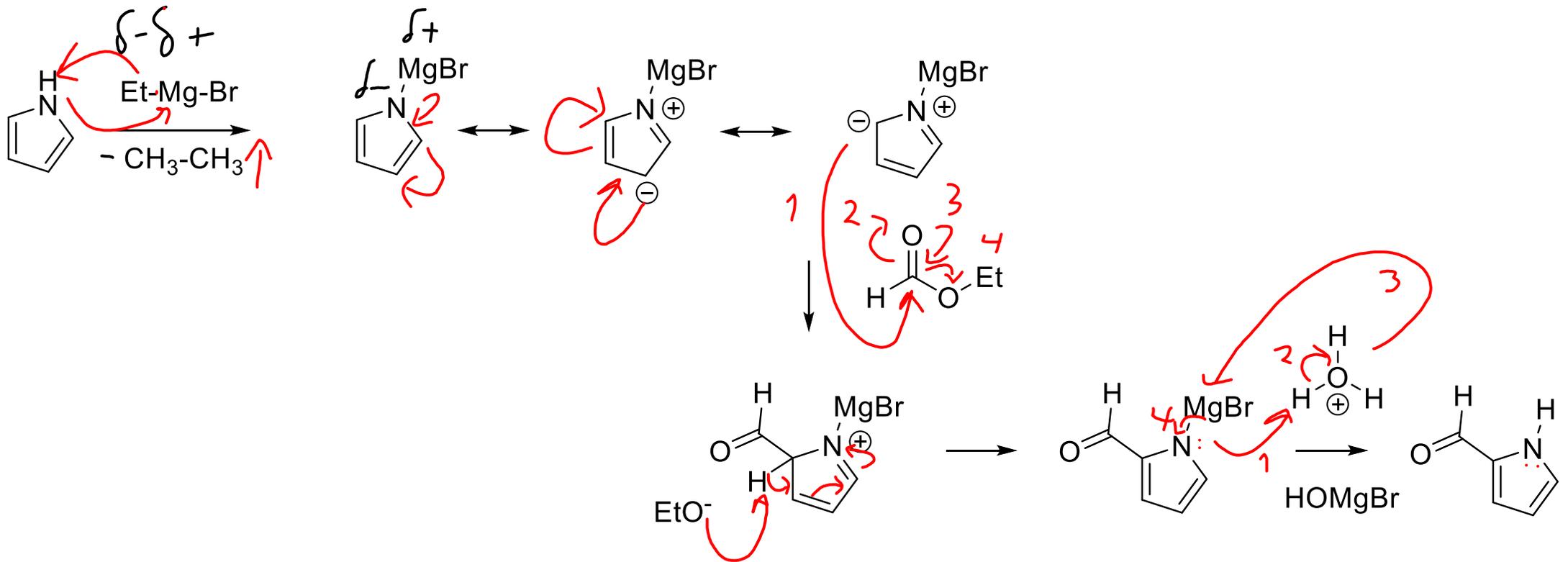
# Metalación con el reactivo de Grignard

$R-Mg-X/\phi-Mg-X$  ( $R-X + Mg/\acute{e}ter \rightarrow R-Mg-X$ )



enlace covalente muy polar,  
pero no iónico, permite la deslocalización  
alrededor del anillo; la sustitución  
se da en los C

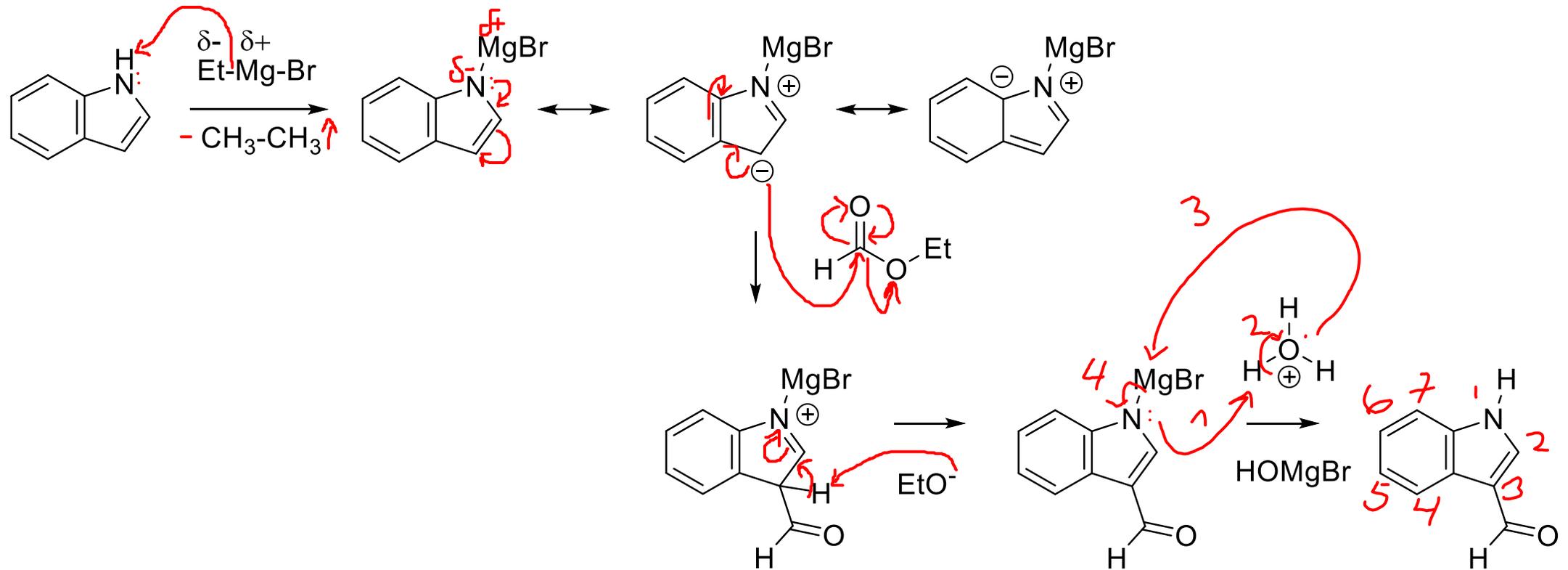
# Metalación con el reactivo de Grignard; $R-Mg-X/\phi-Mg-X$ ( $R-X + Mg/\acute{e}ter \rightarrow R-Mg-X$ ) Sustitución en los $(C_2)$



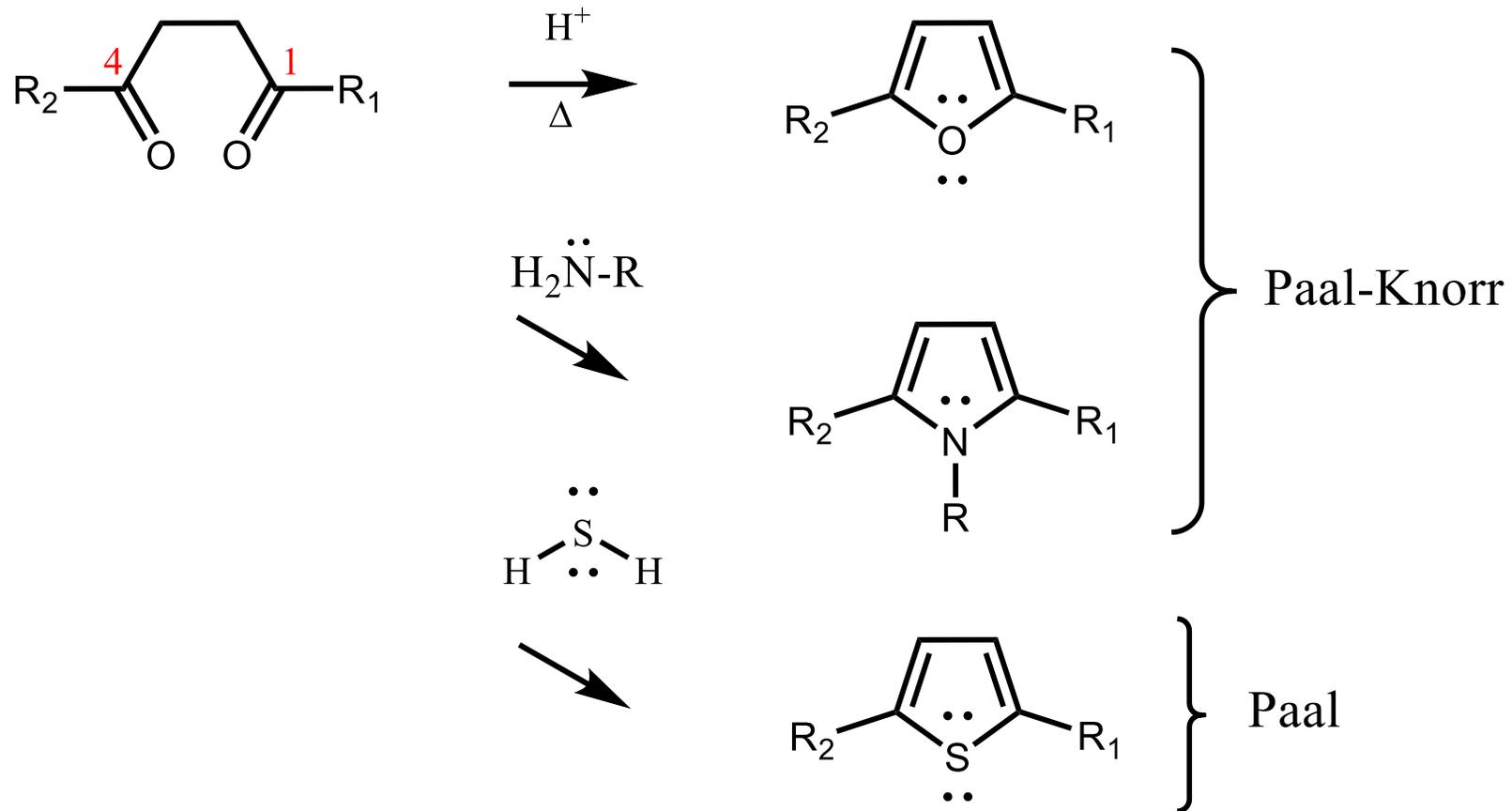
# Metalación con el reactivo de Grignard

$R-Mg-X/\phi-Mg-X$  ( $R-X + Mg/\acute{e}ter \rightarrow R-Mg-X$ )

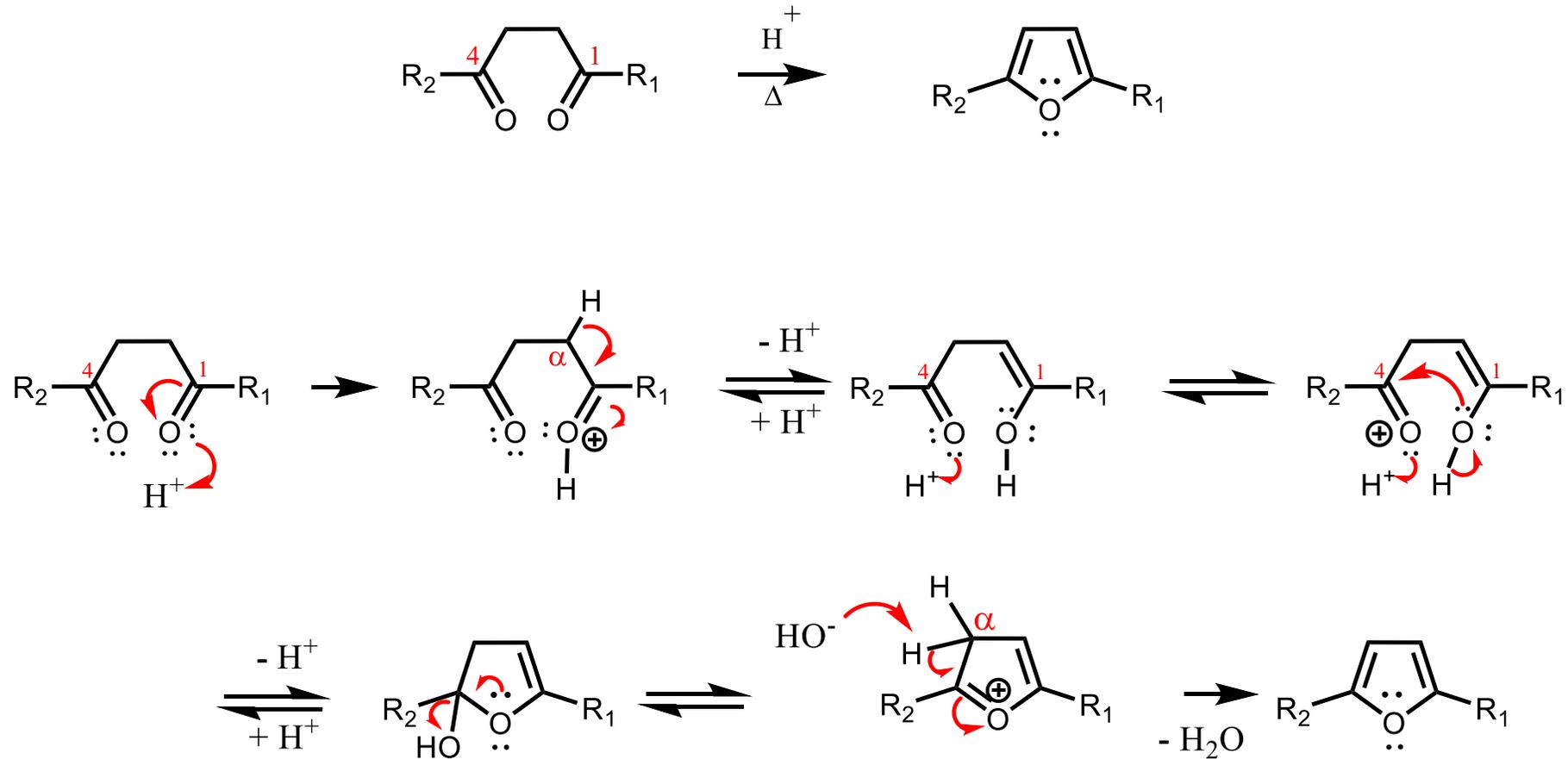
- Sustitución en C3



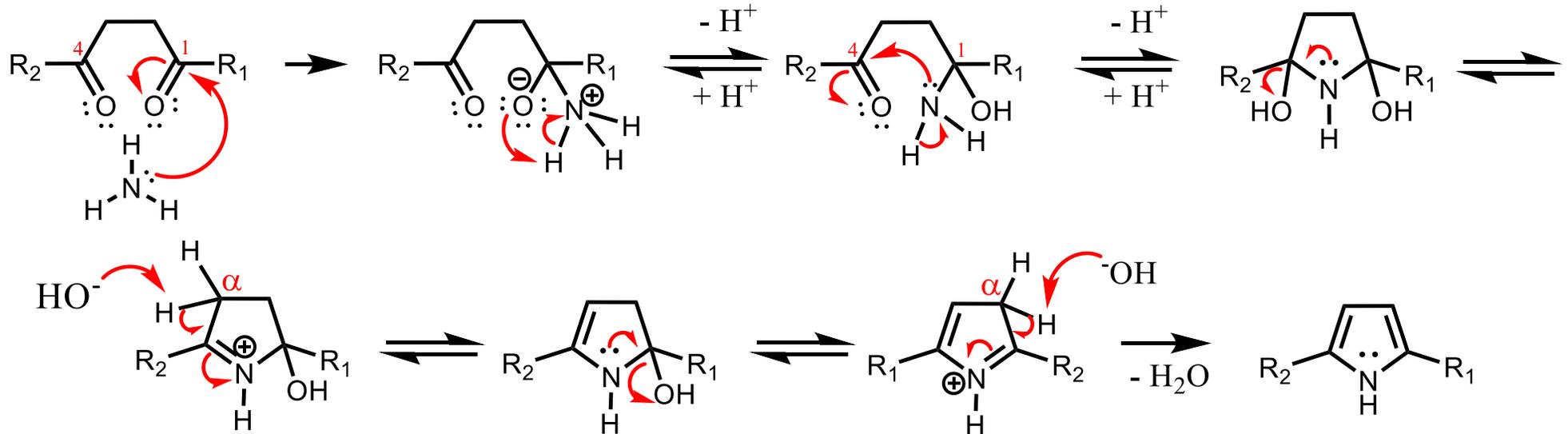
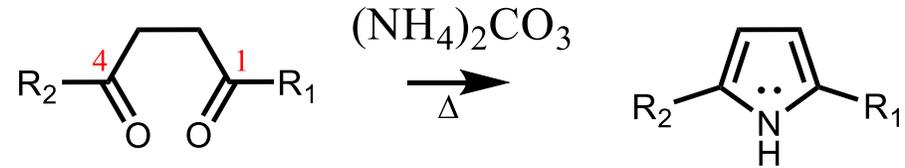
# Síntesis generales: Paal-Knorr y Paal



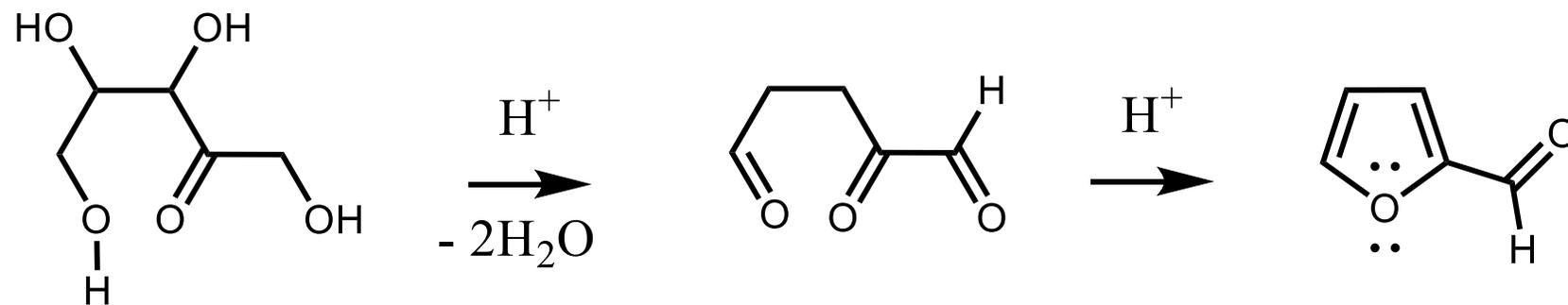
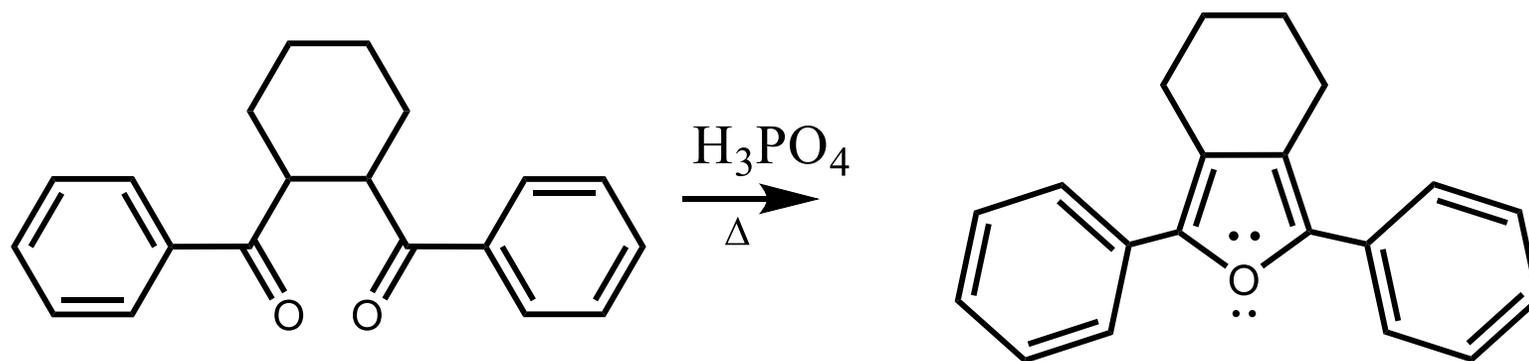
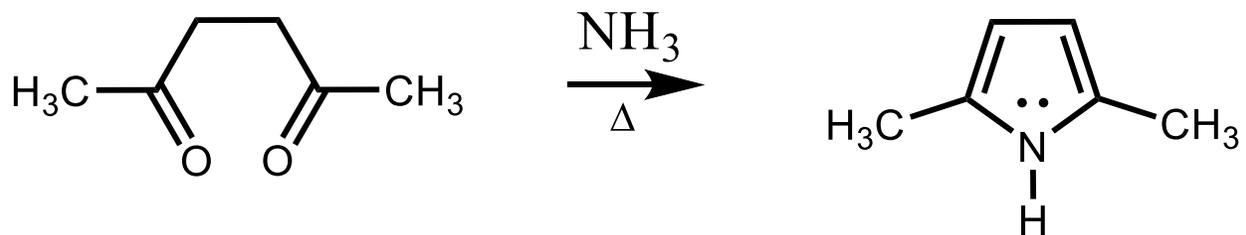
# Mecanismos de síntesis generales: Paal-Knorr



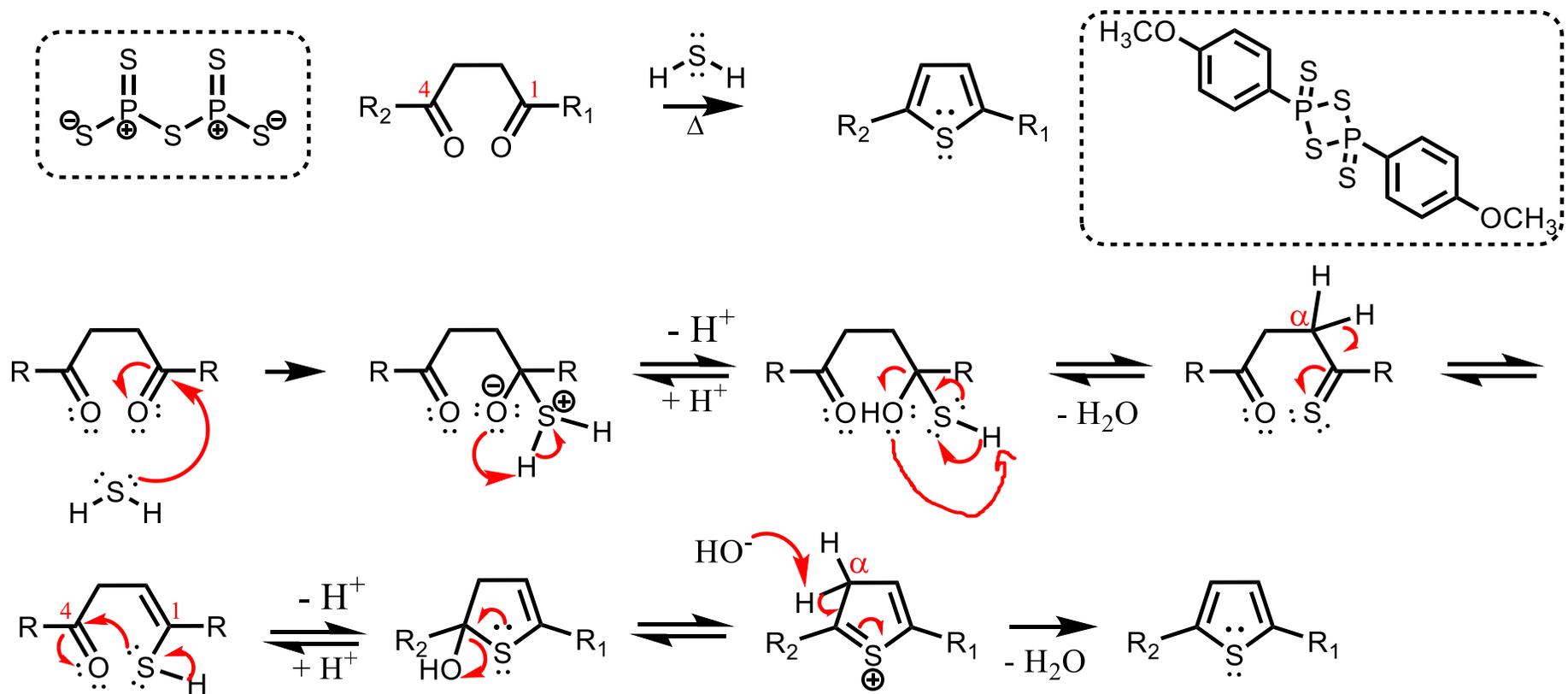
# Mecanismos de síntesis generales: Paal-Knorr



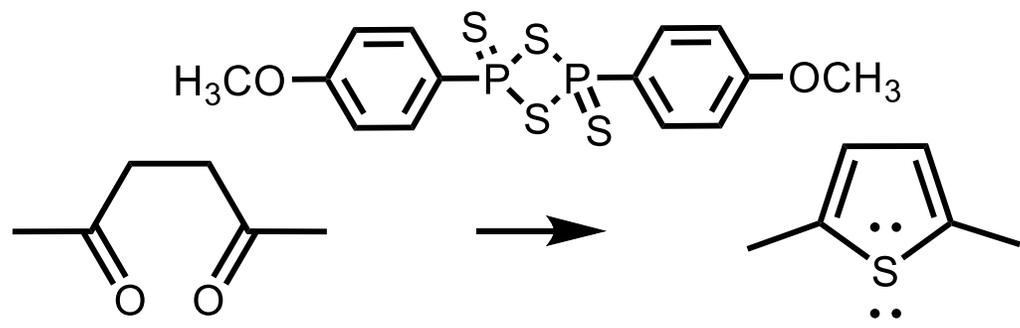
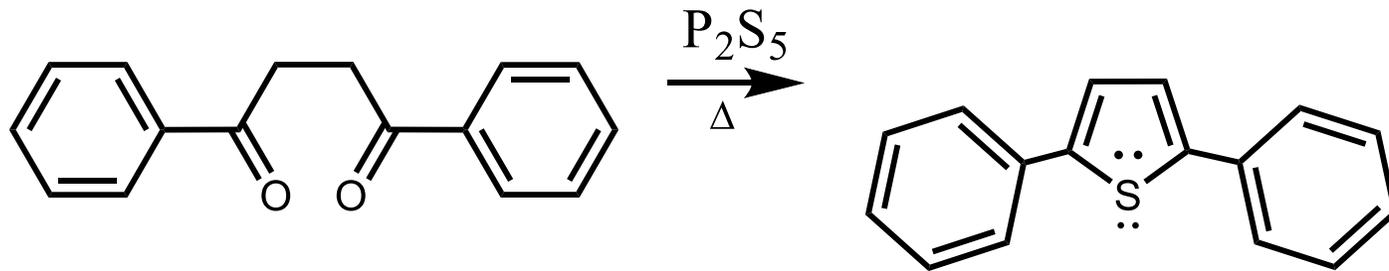
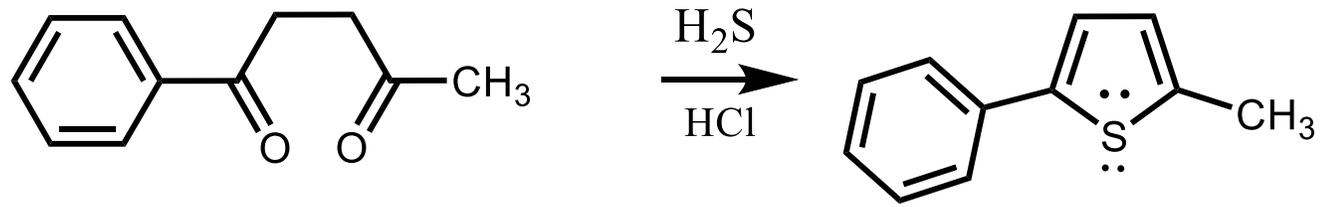
# Síntesis de Paal-Knorr



# Mecanismos de síntesis generales: Paal

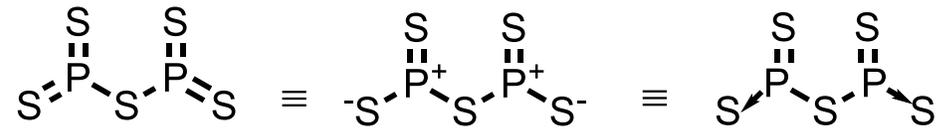
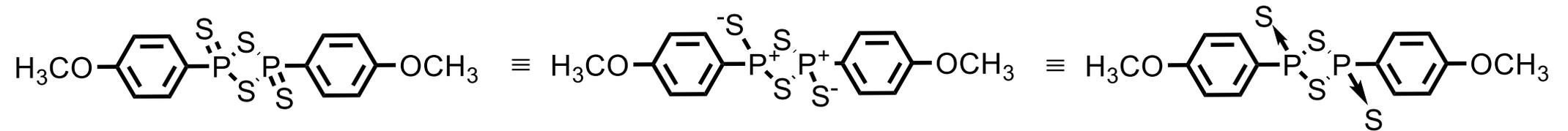


# Síntesis de Paal

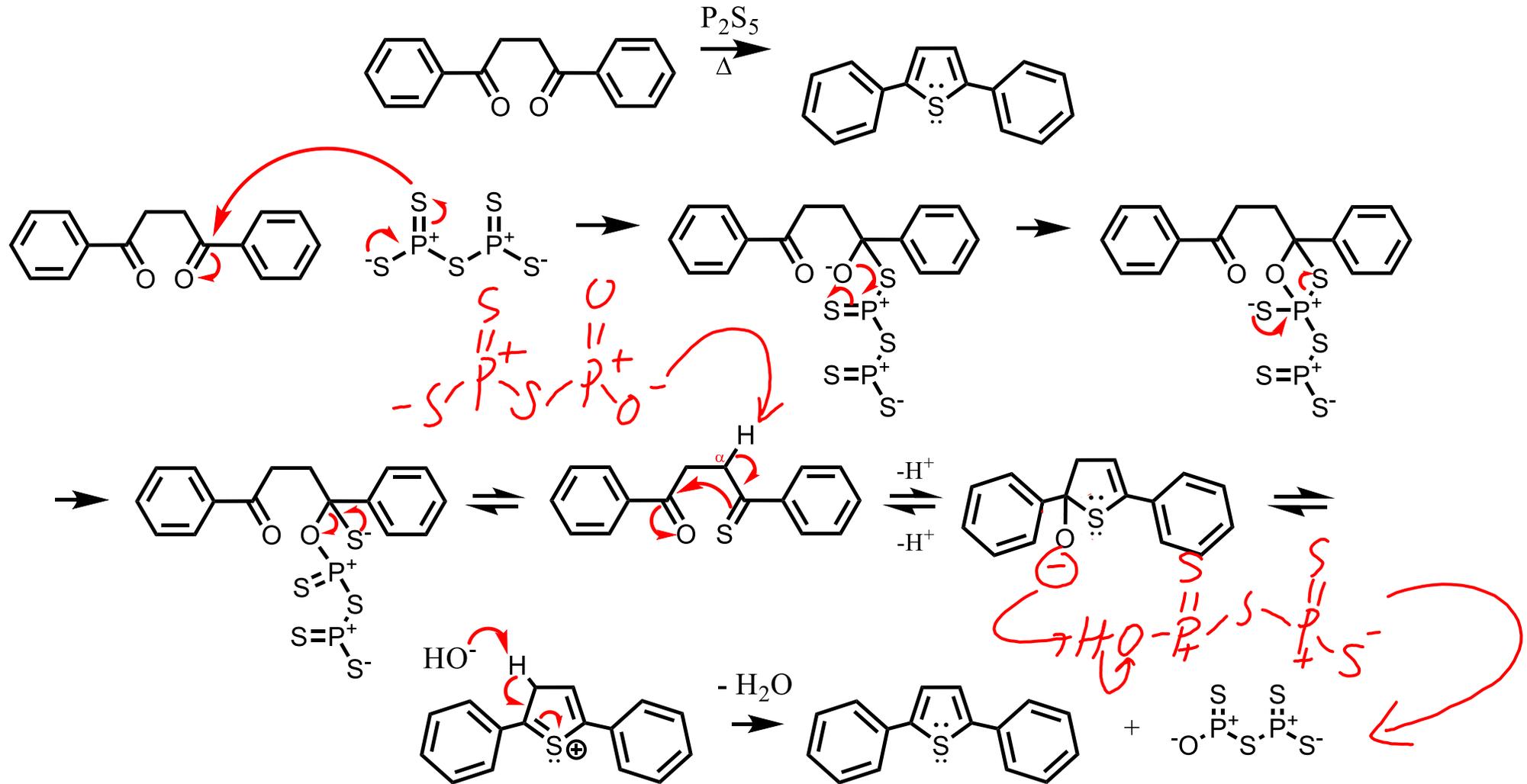


# Síntesis de heterociclos azufrados: tiofenos

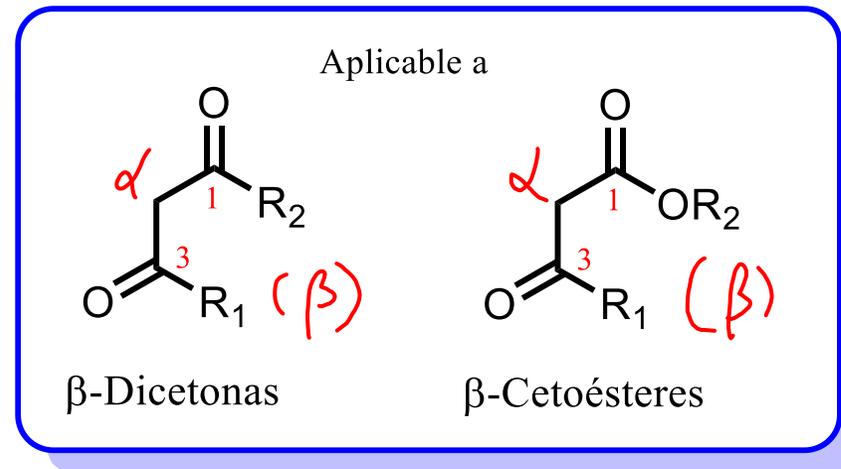
Se emplea reactivo de Lawesson o pentasulfuro de fósforo



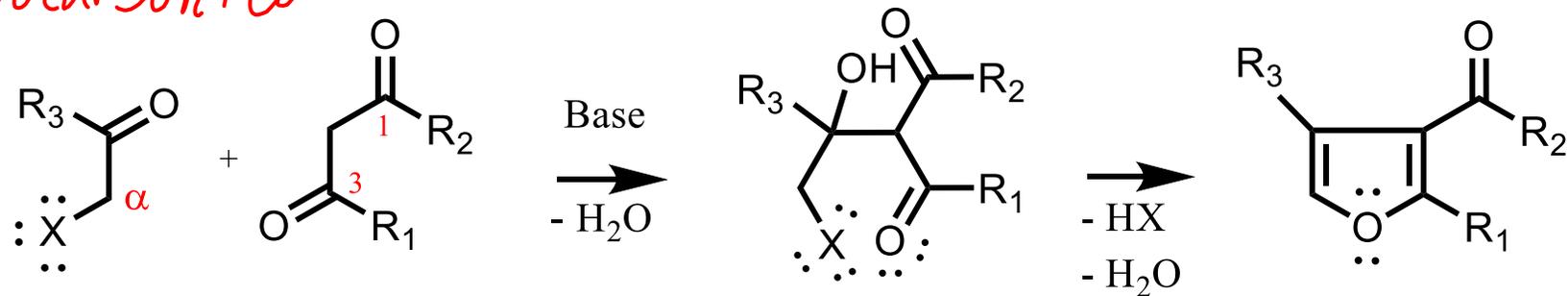
# Síntesis de tiofenos



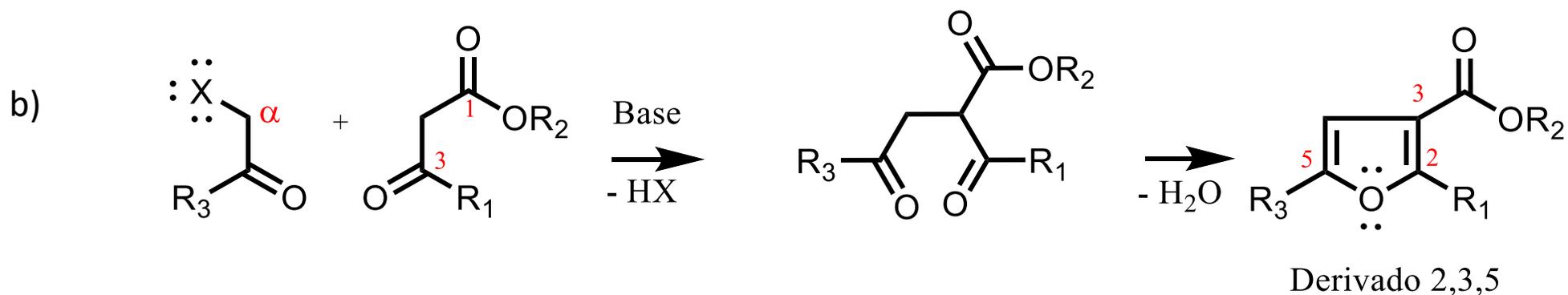
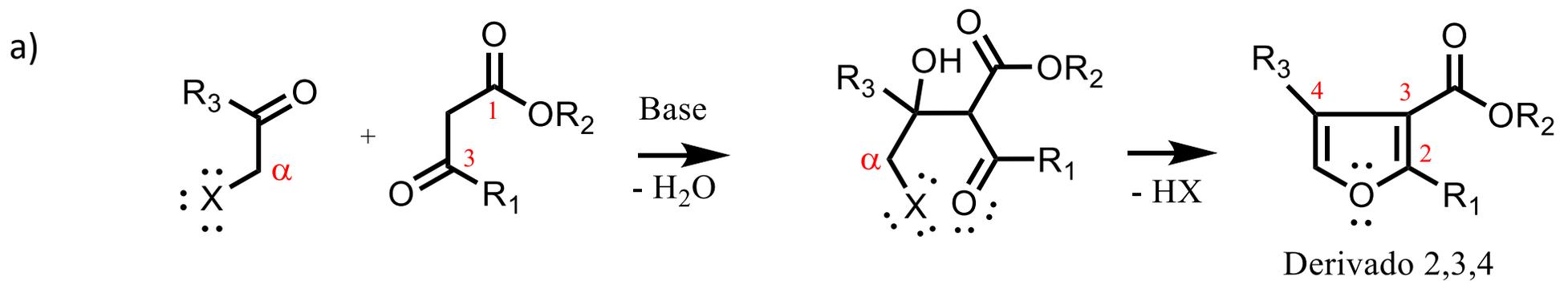
# Síntesis de furanos: Feist-Benary



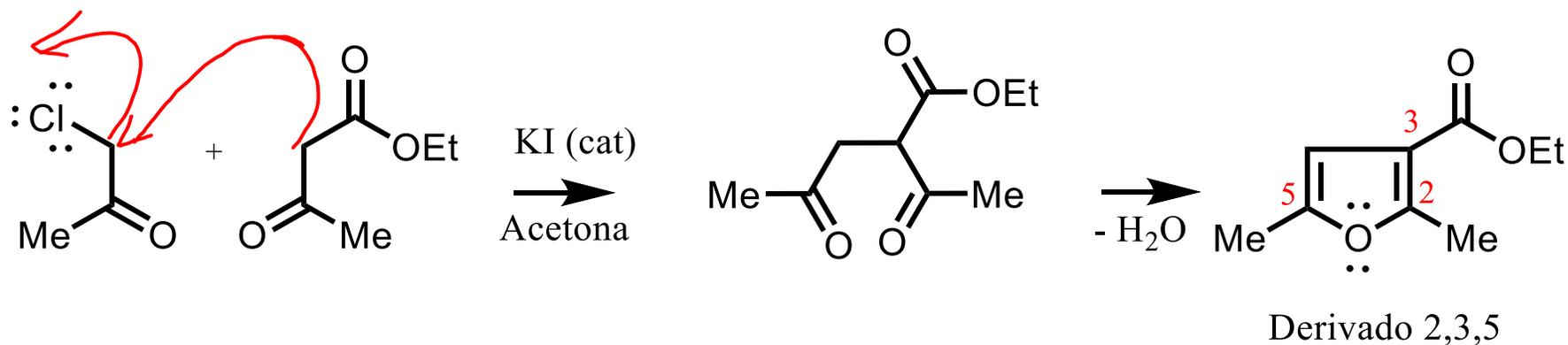
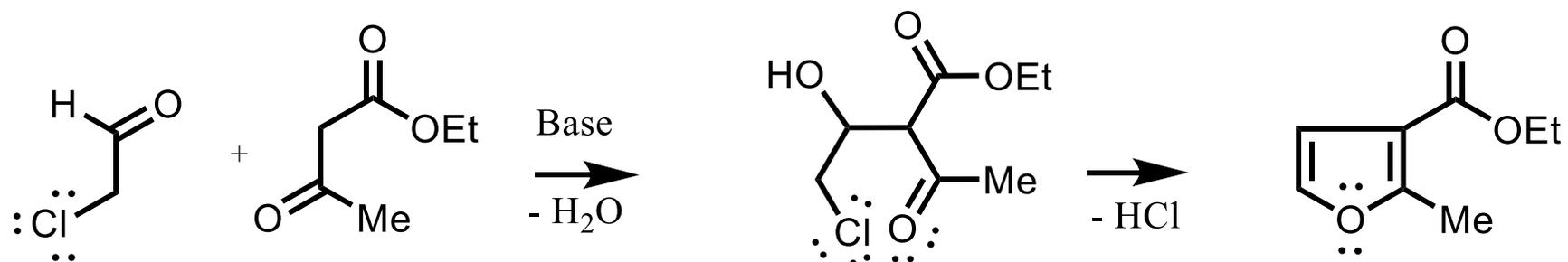
*$\alpha$ -Halocarbonilo*



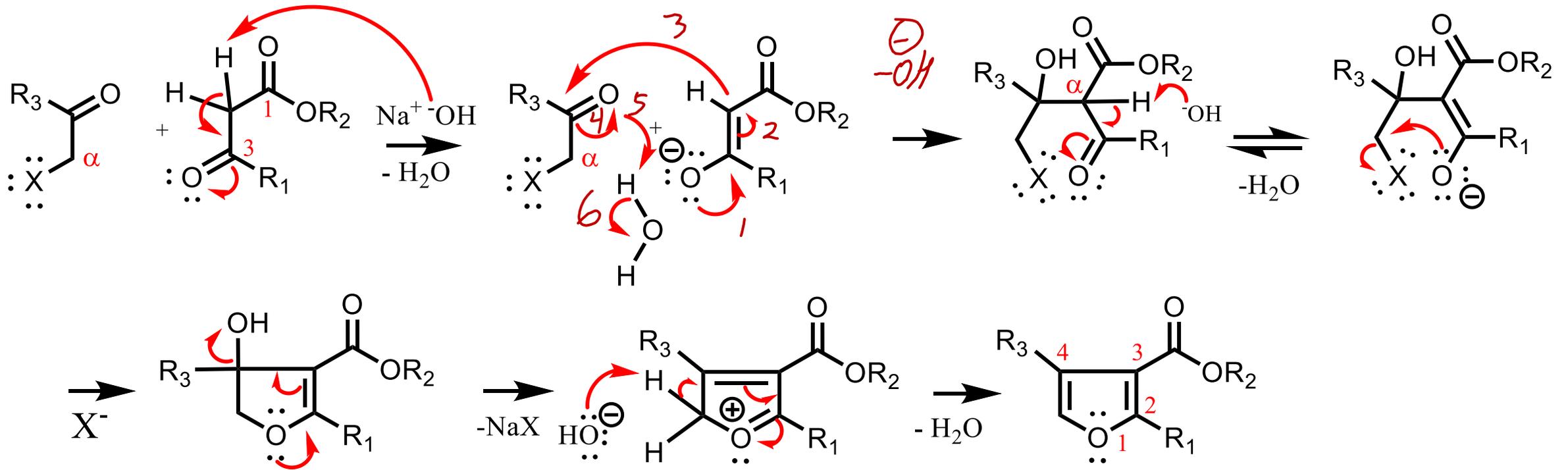
# Feist-Benary, dos posibilidades (a y b) cuando el 1,3-dicarbonilo es un éster



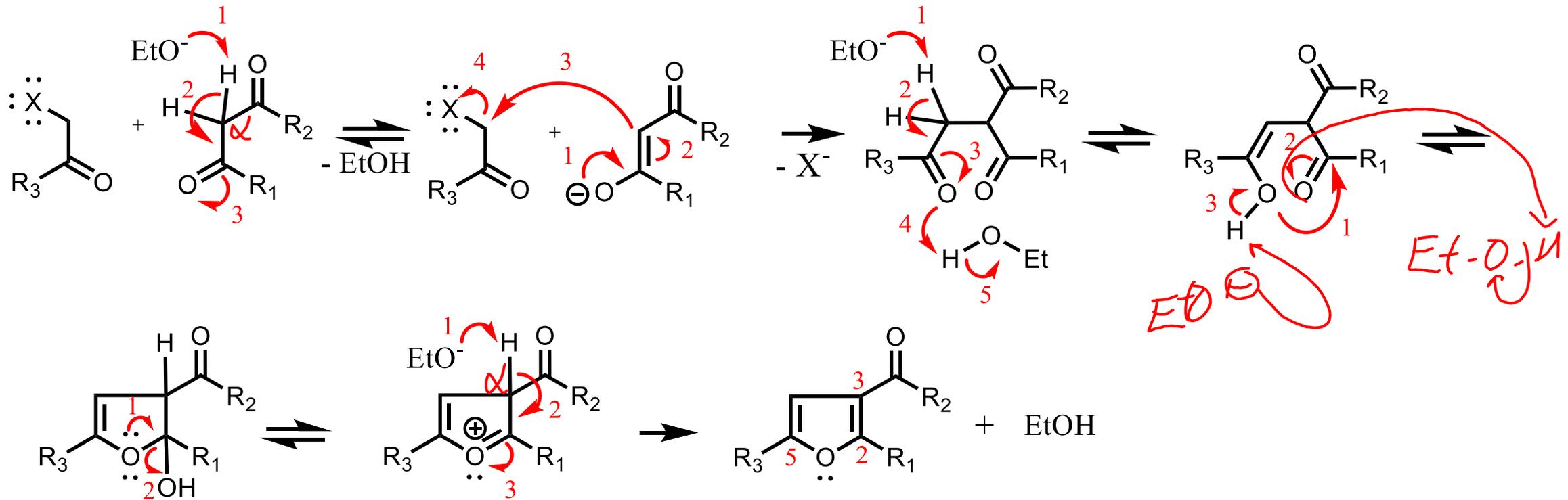
# Feist-Benary, dos posibilidades cuando el 1,3-dicarbonilo es un éster



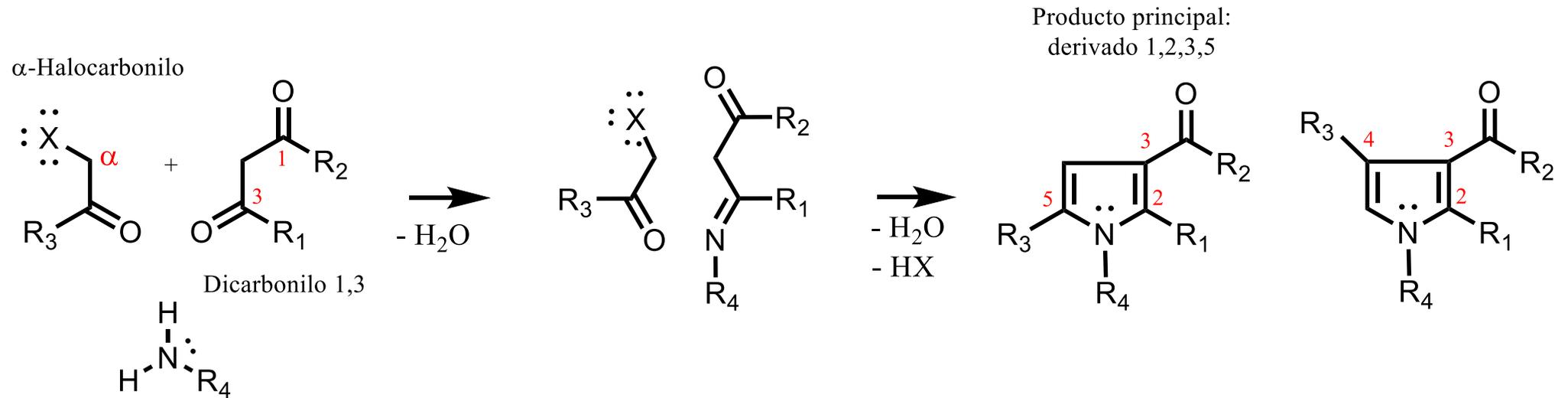
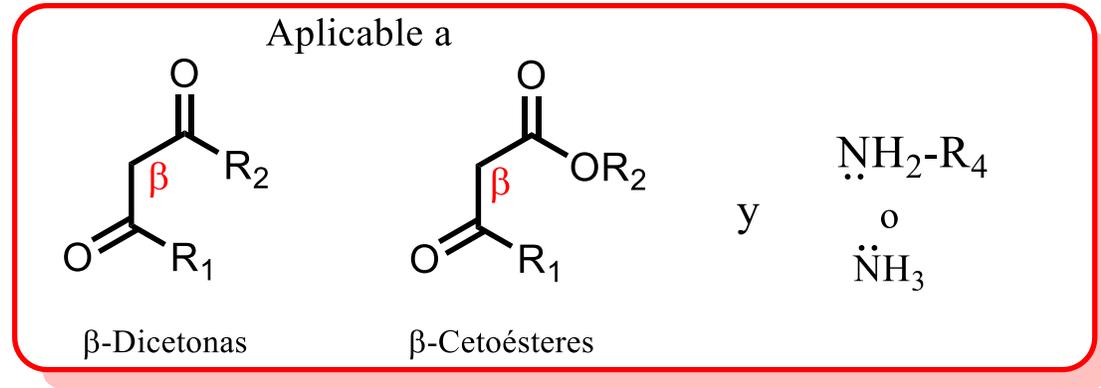
# Feist-Benary $\rightarrow$ Derivado 2,3,4



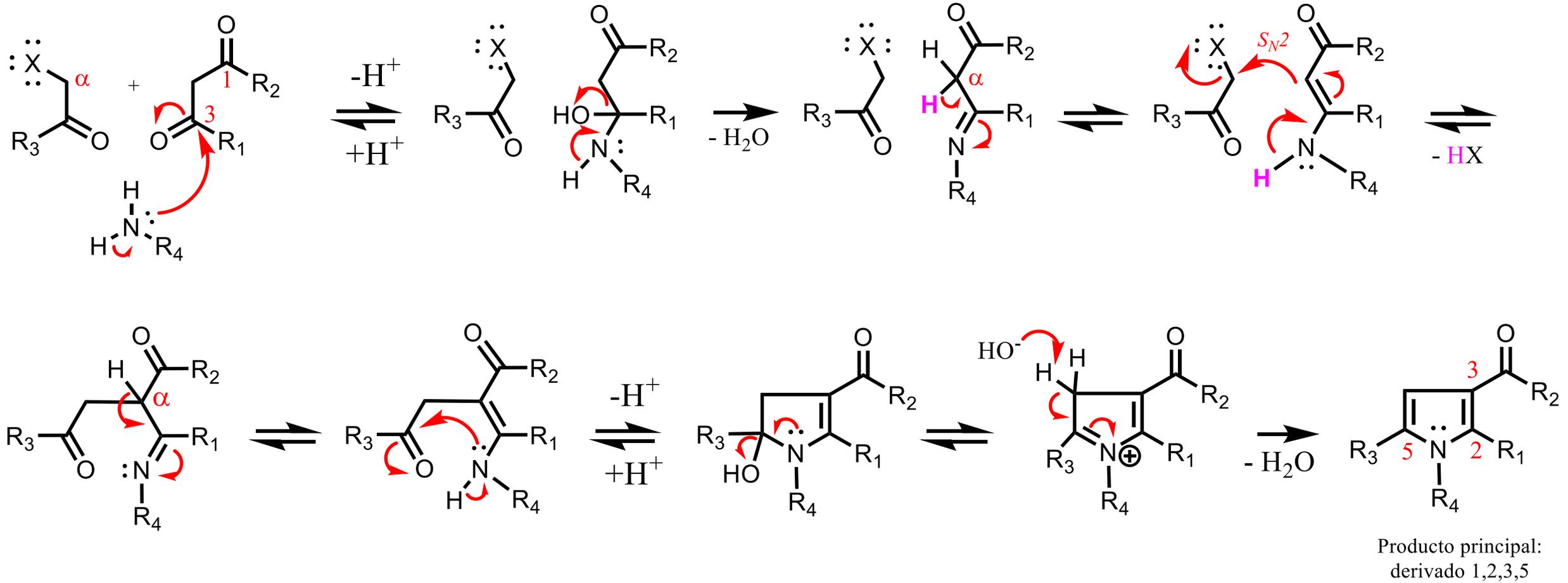
# Feist-Benary → Derivado 2,3,5



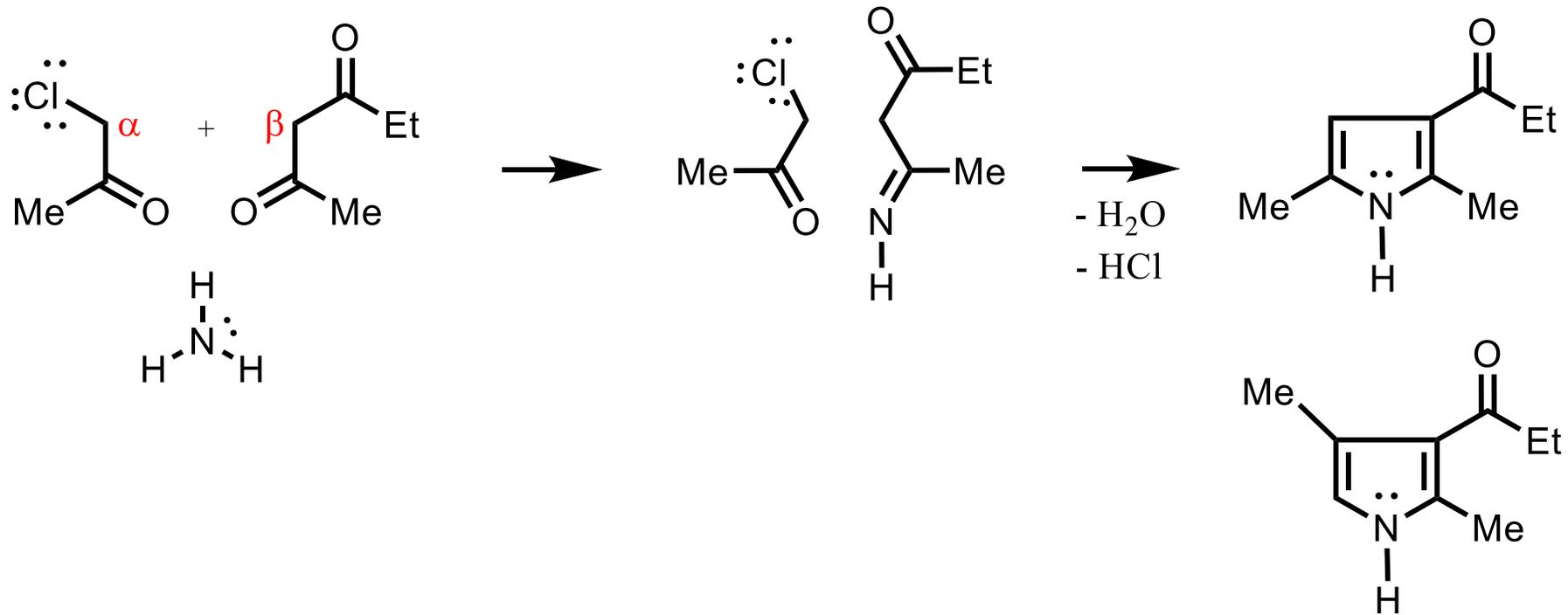
# Síntesis de Hantzsch



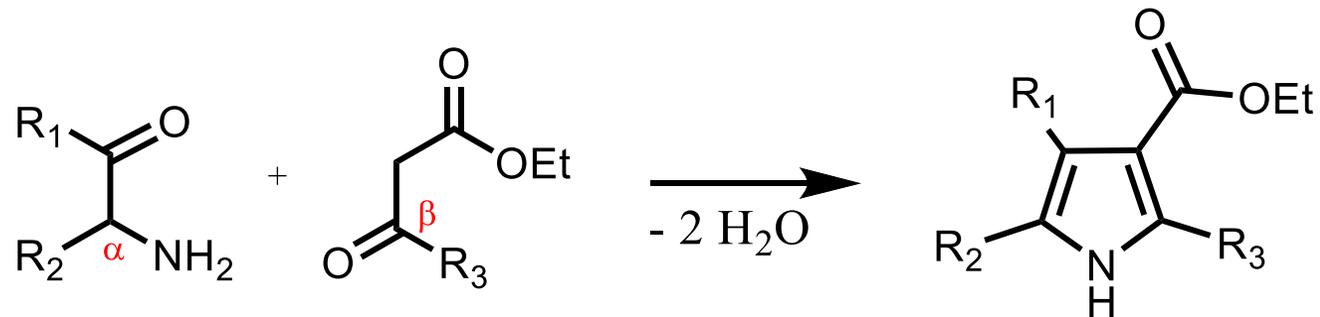
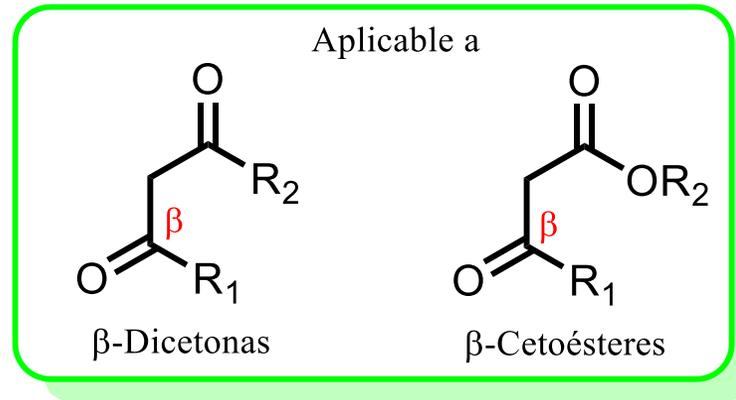
# Síntesis de Hantzsch



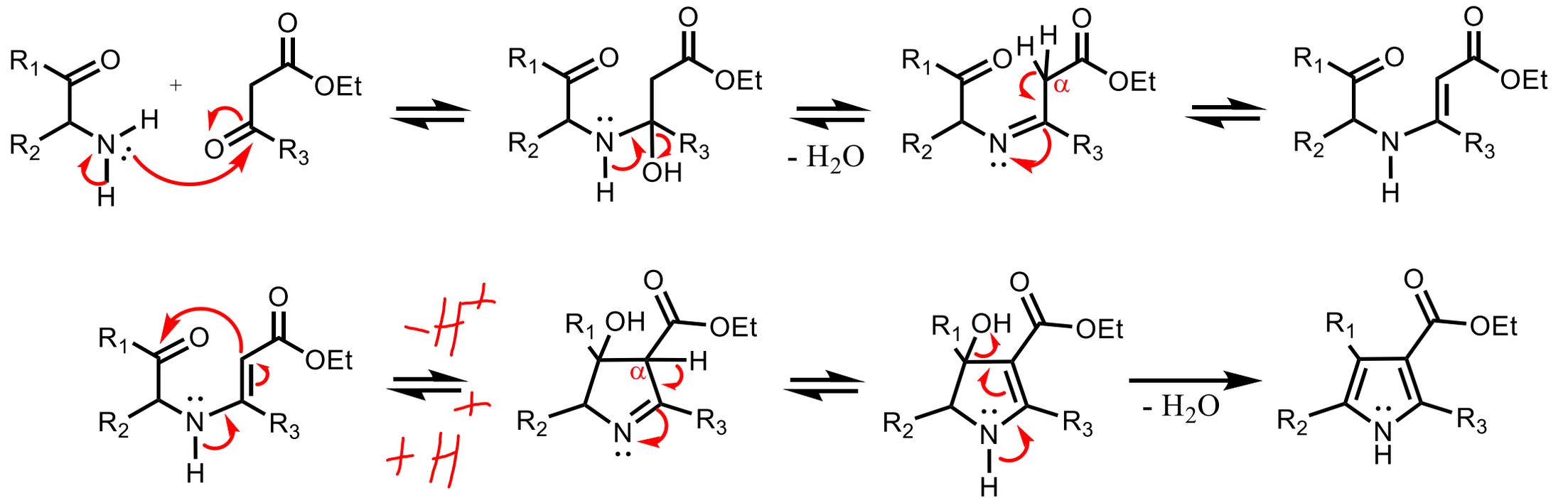
# Síntesis de Hantzsch: ejemplos



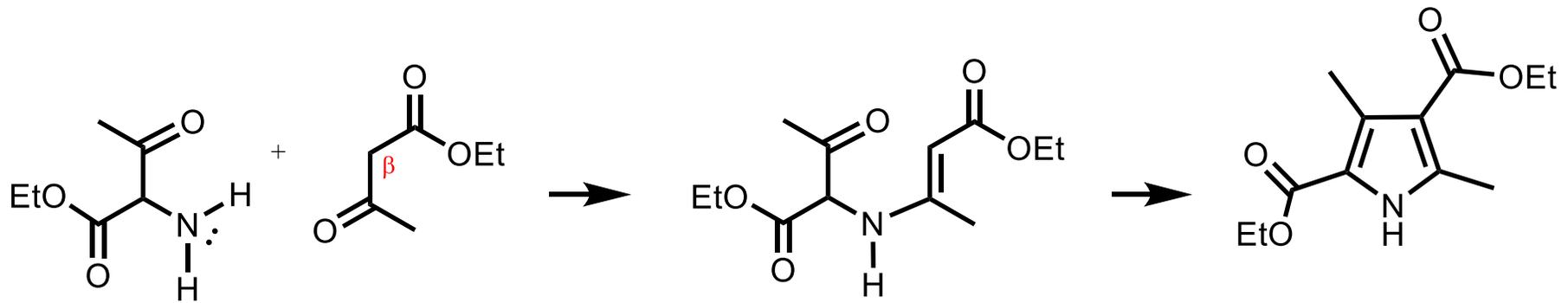
# Síntesis de Knorr



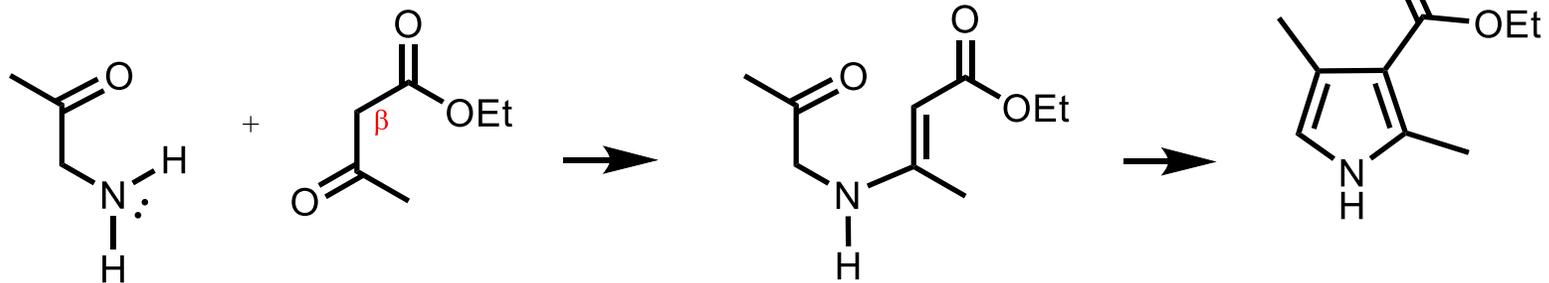
# Síntesis de Knorr



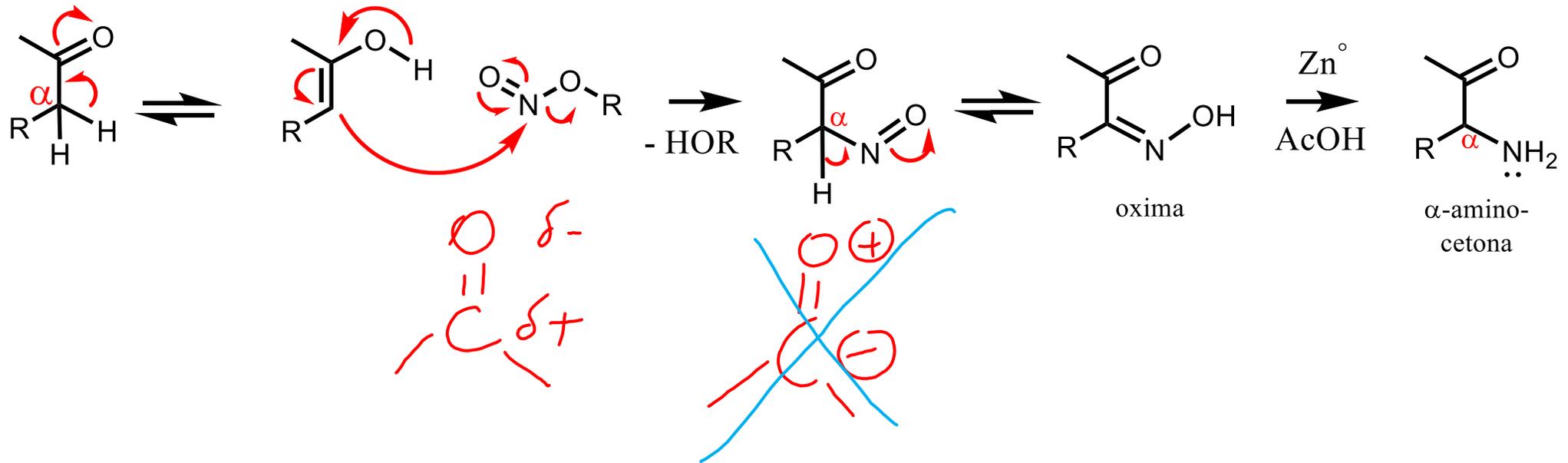
# Síntesis de Knorr: ejemplos



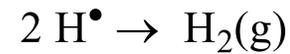
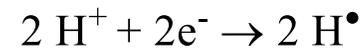
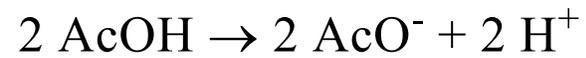
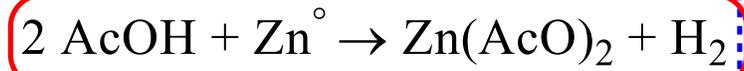
*$\alpha$ -aminocetona*



# Síntesis de Knorr, formación de $\alpha$ -aminocetonas

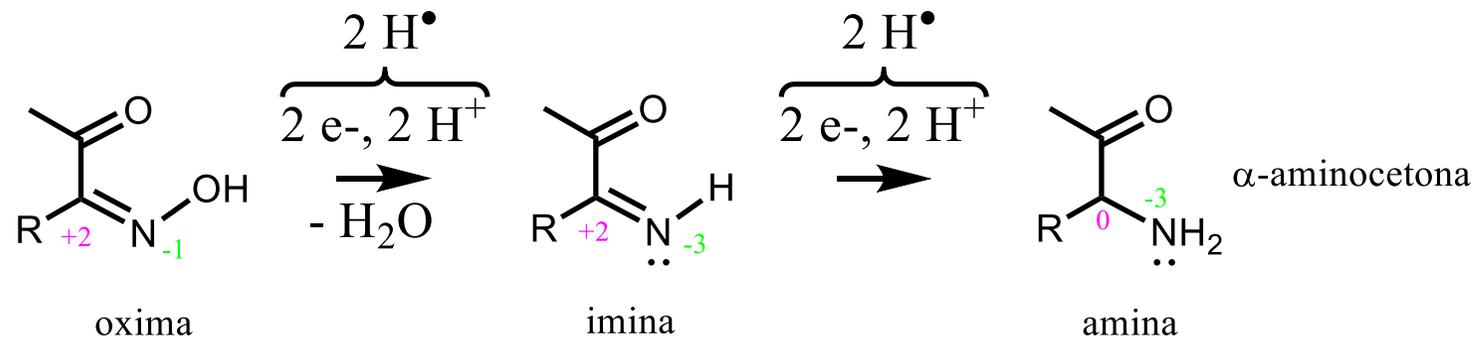


# Síntesis de Knorr, formación de $\alpha$ -aminocetonas

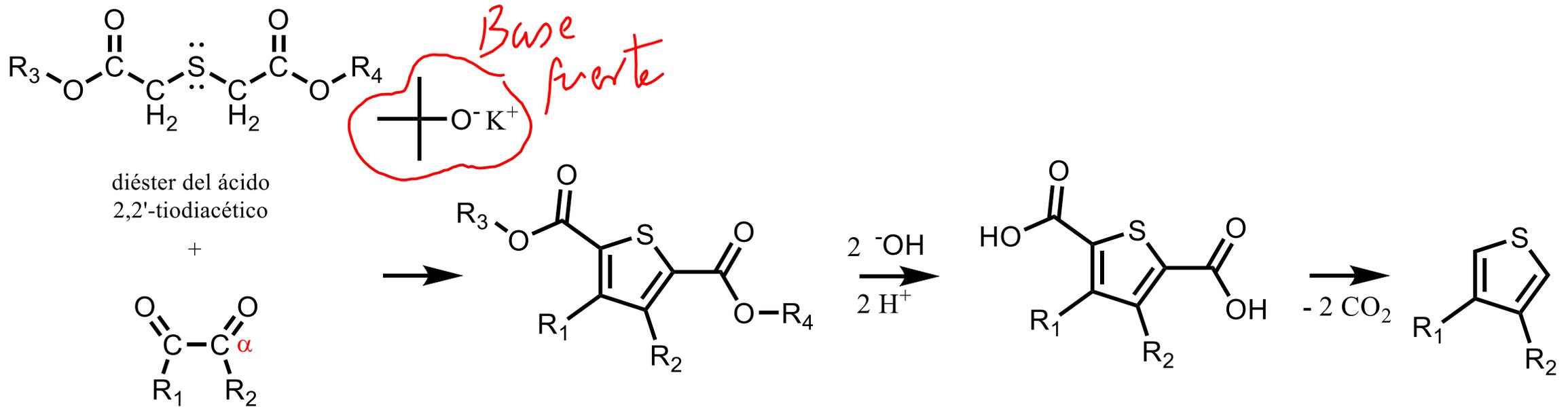


#Ox. C;

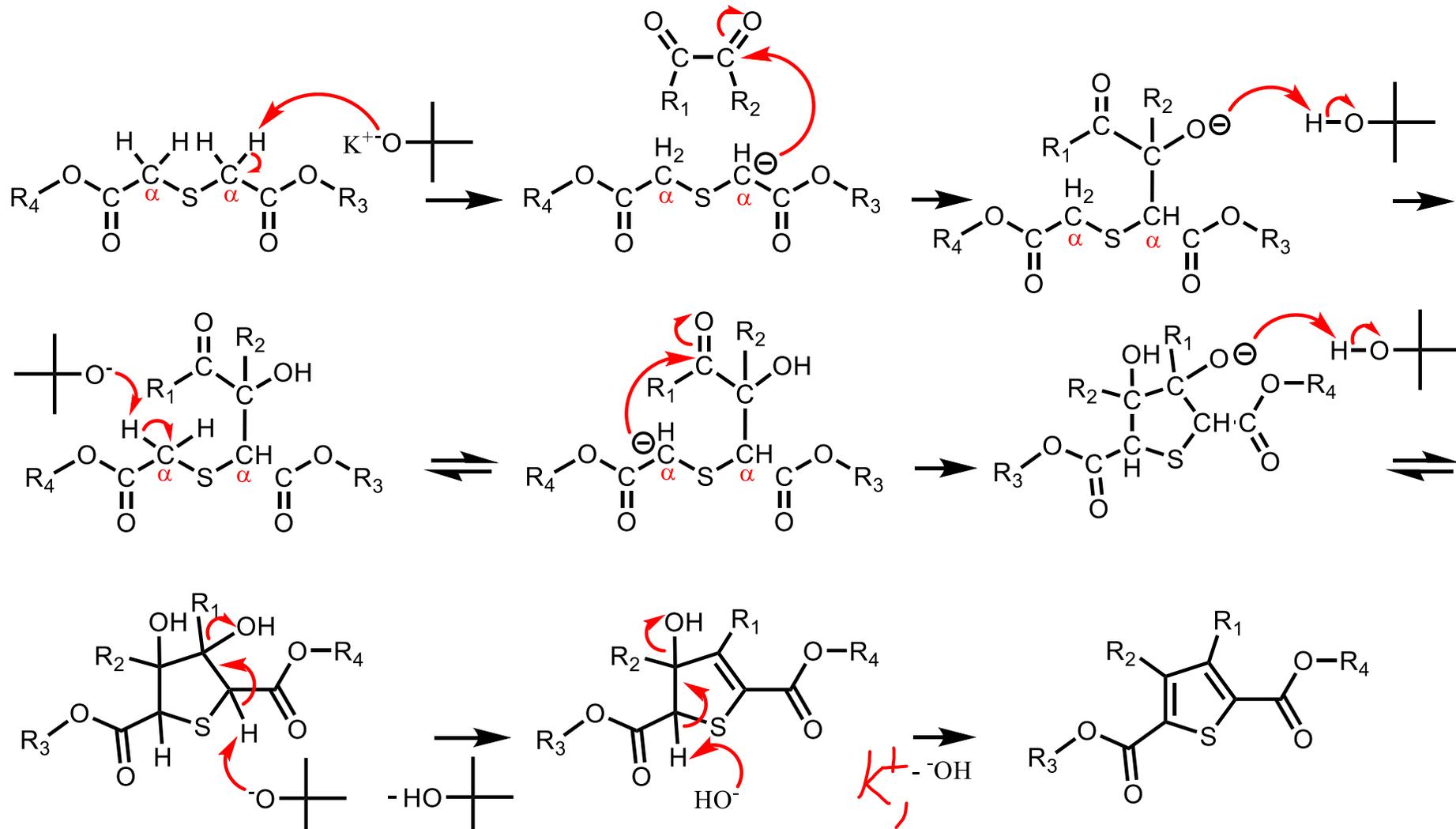
#Ox. N



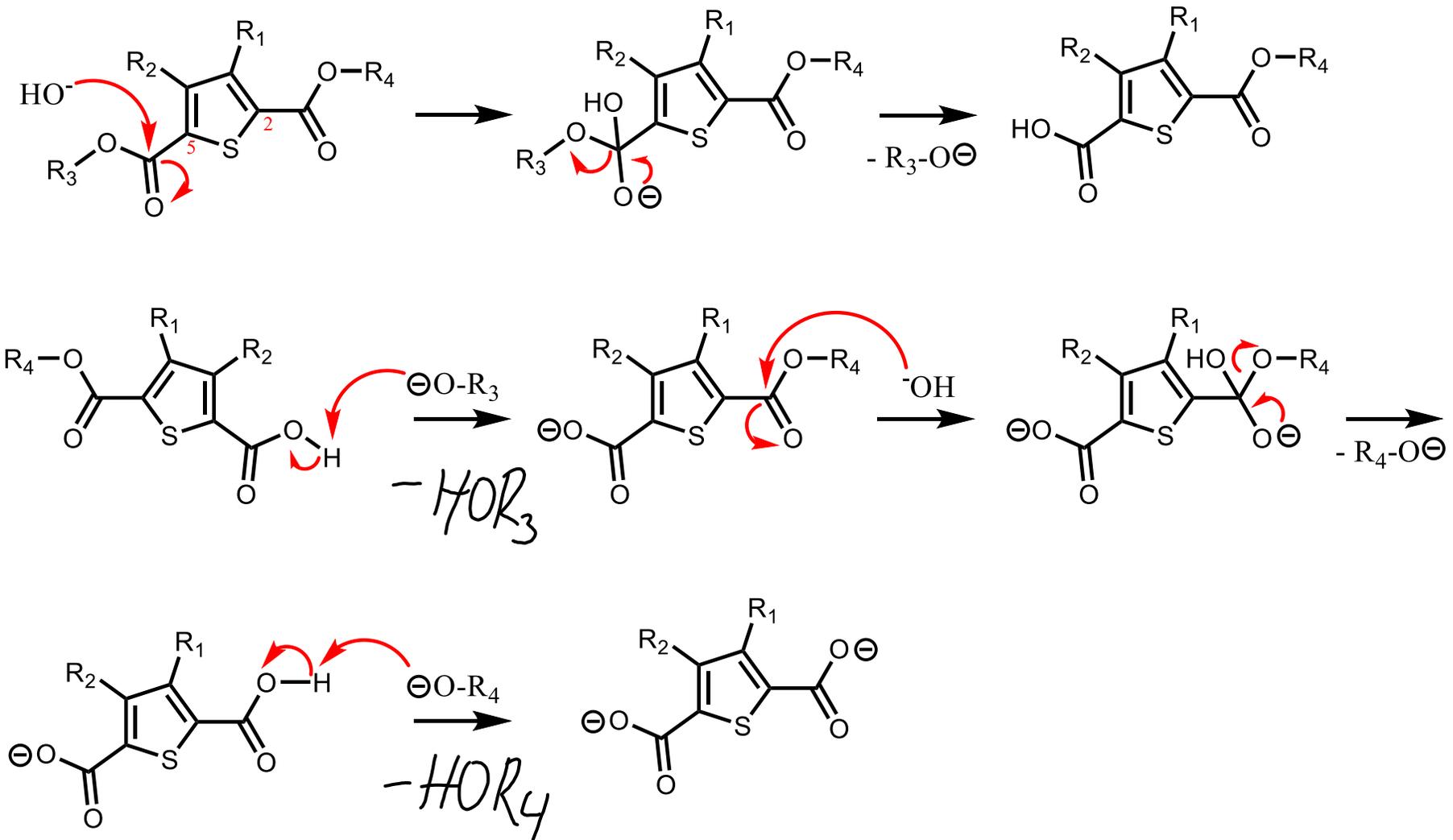
# Síntesis de Hinsberg



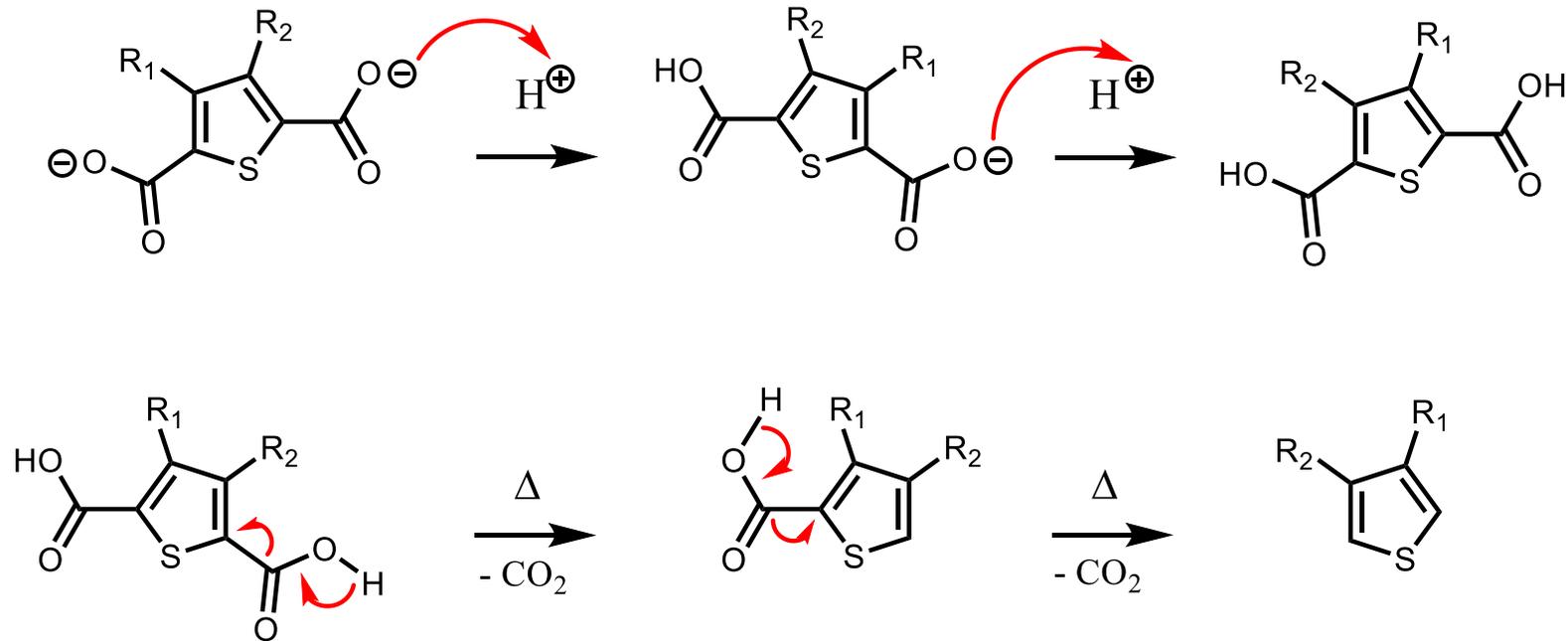
# Mecanismo de Hinsberg



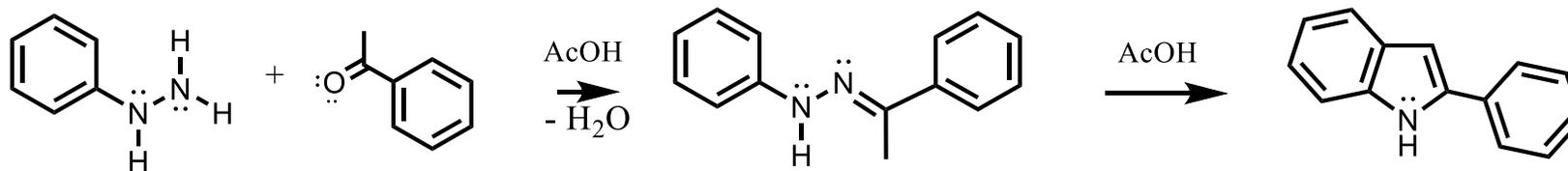
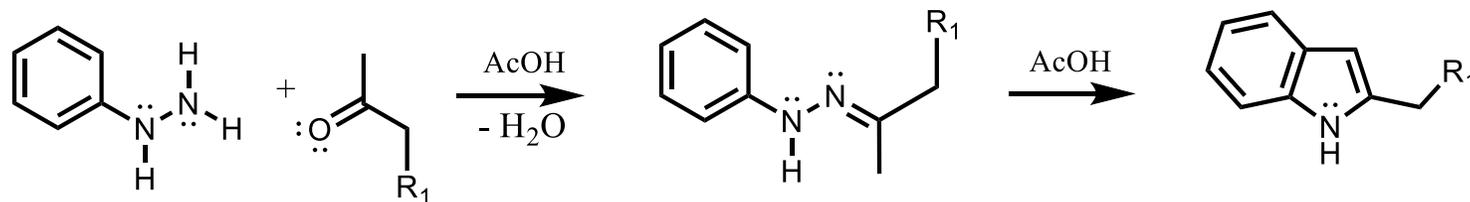
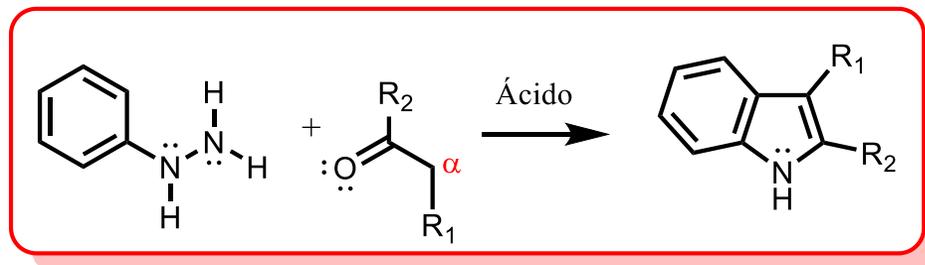
# Hidrólisis del 2,5-tiofendicarboxilato



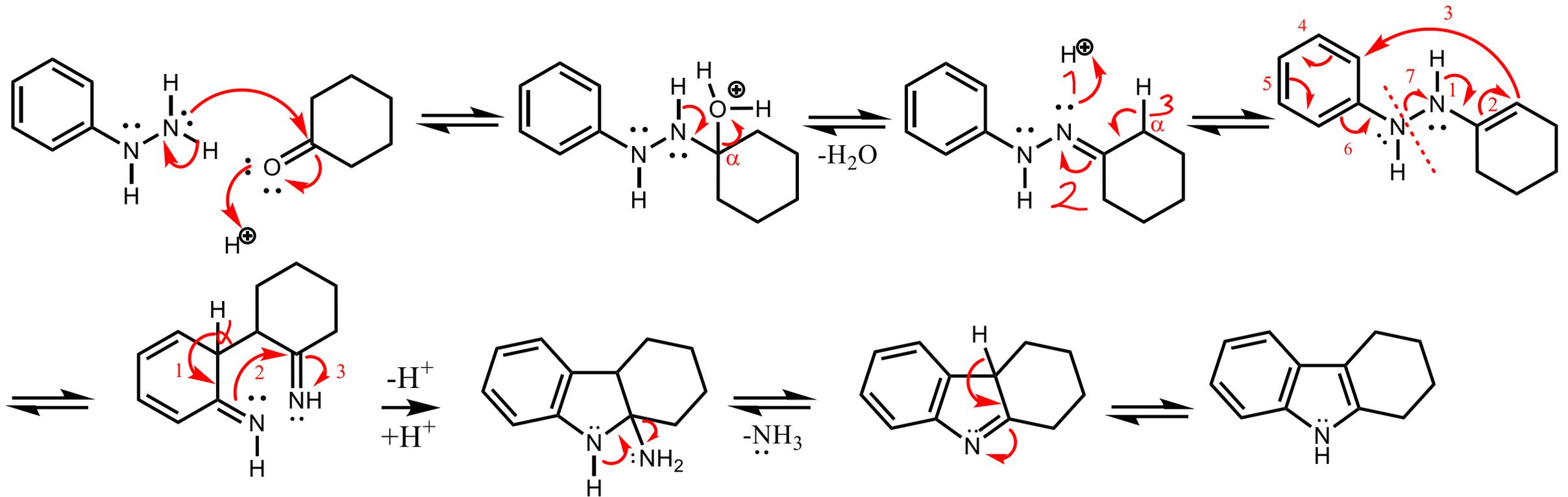
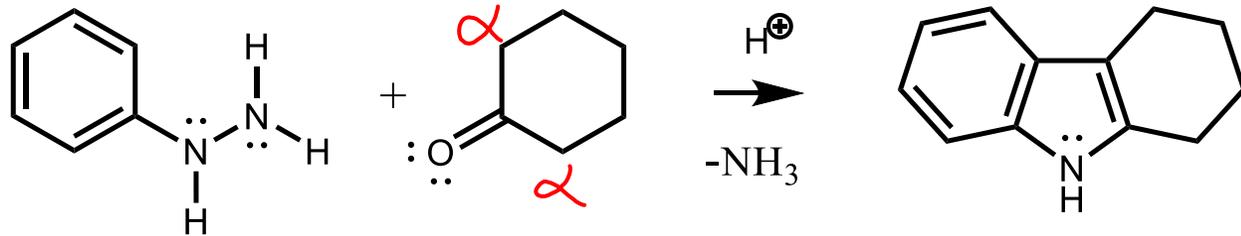
# Descarboxilación del 2,5-tiofendicarboxilato



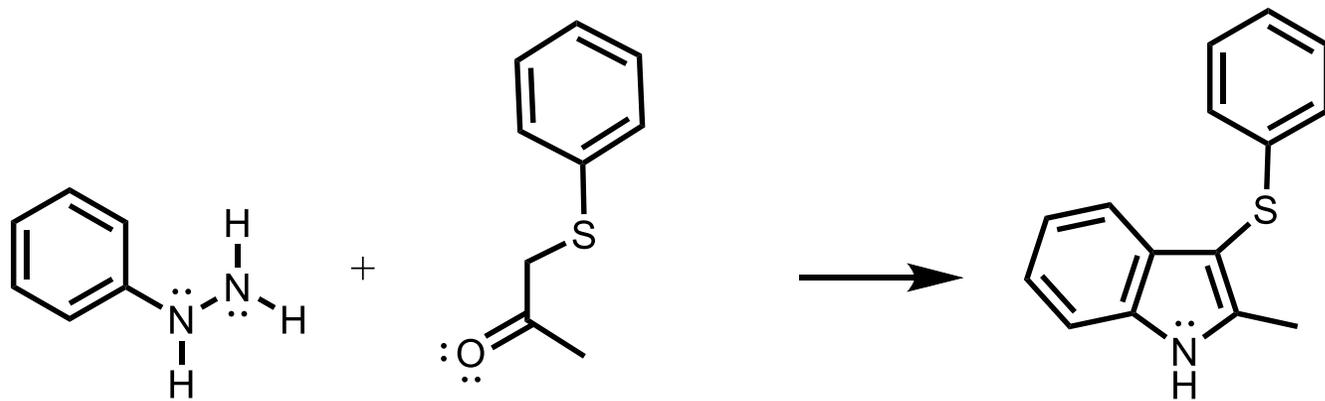
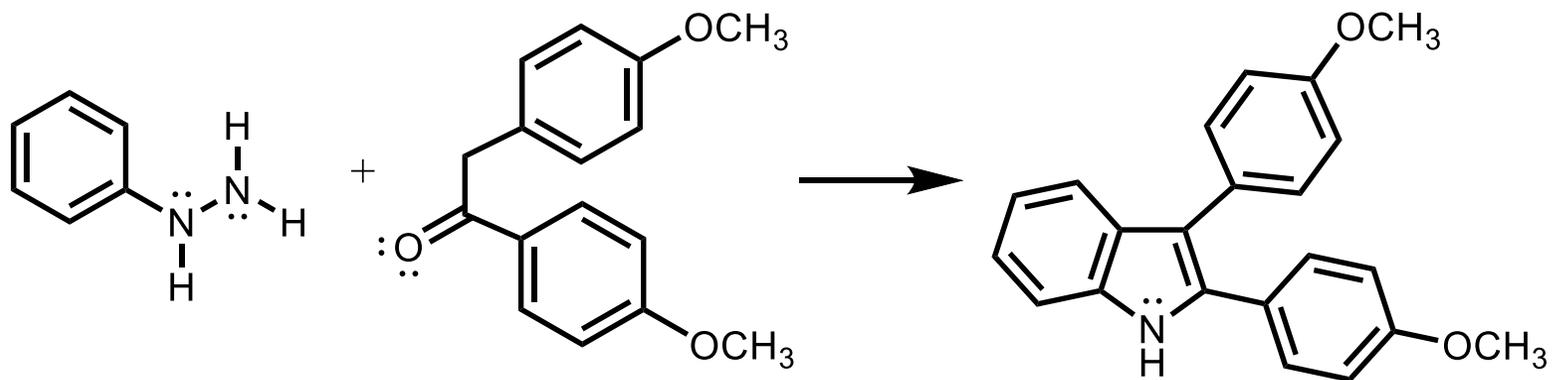
# Síntesis de indoles: Fischer



# Mecanismo de indoles de Fischer

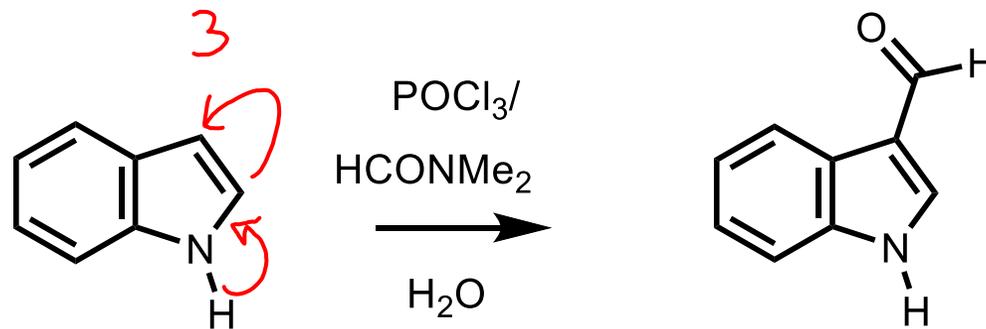
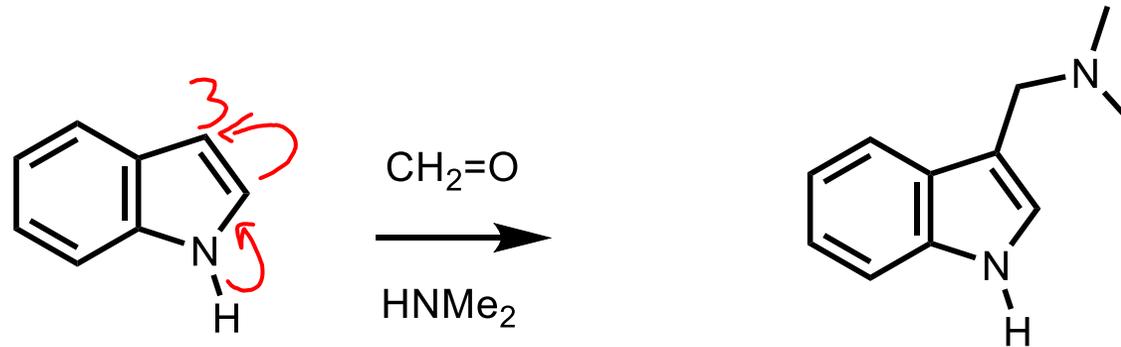


# Síntesis de indoles

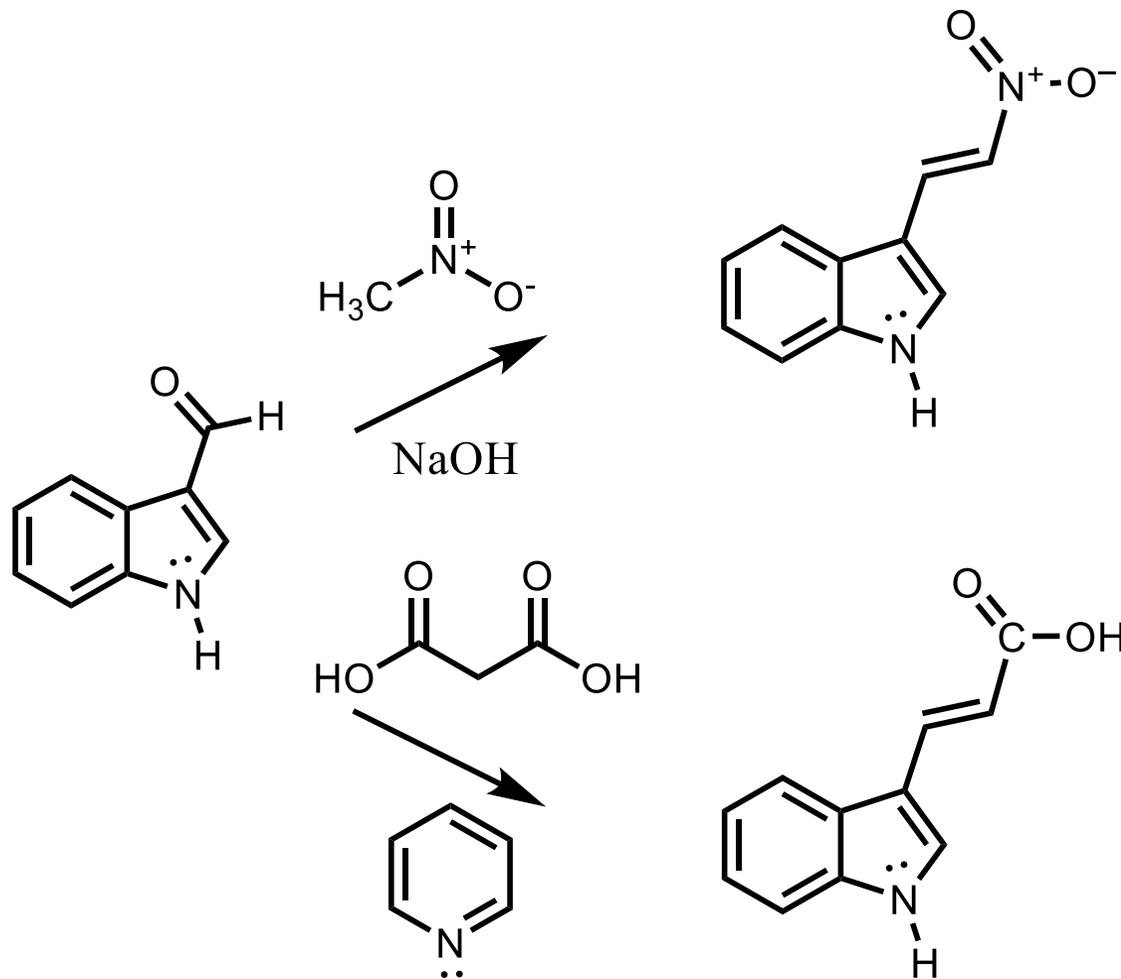


# Indoles

## reactividad general

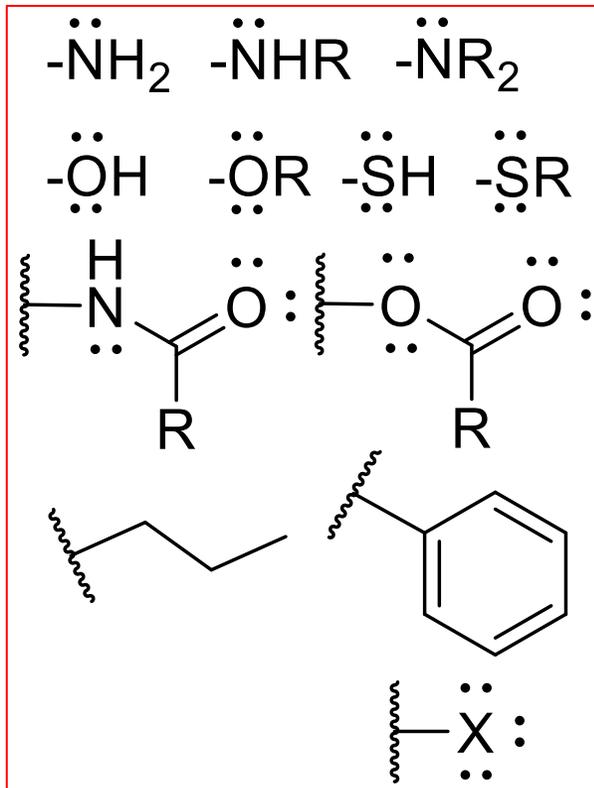


# Indoles: ejemplos de reactividad general

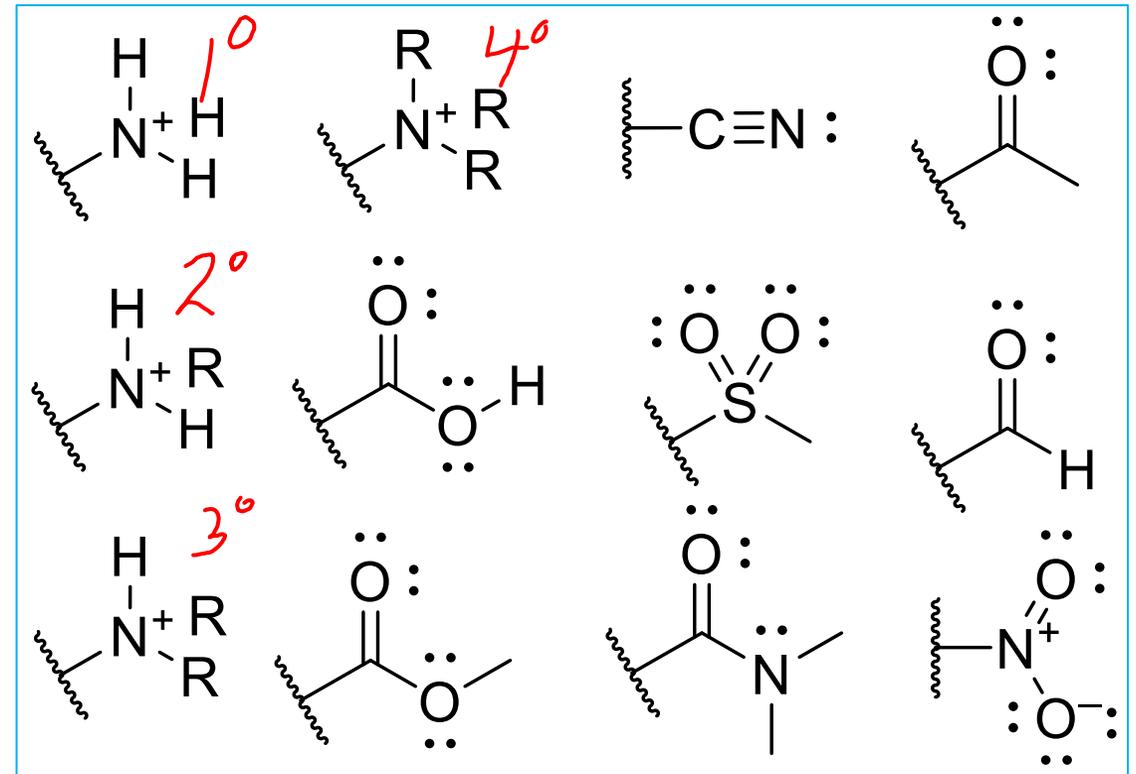


# Grupos (orientadores) que afectan la SEA

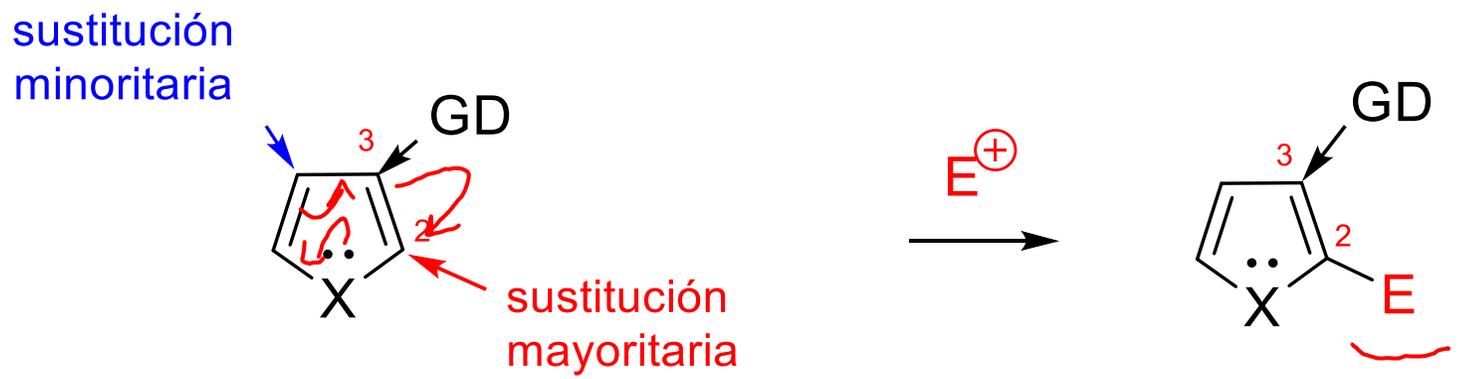
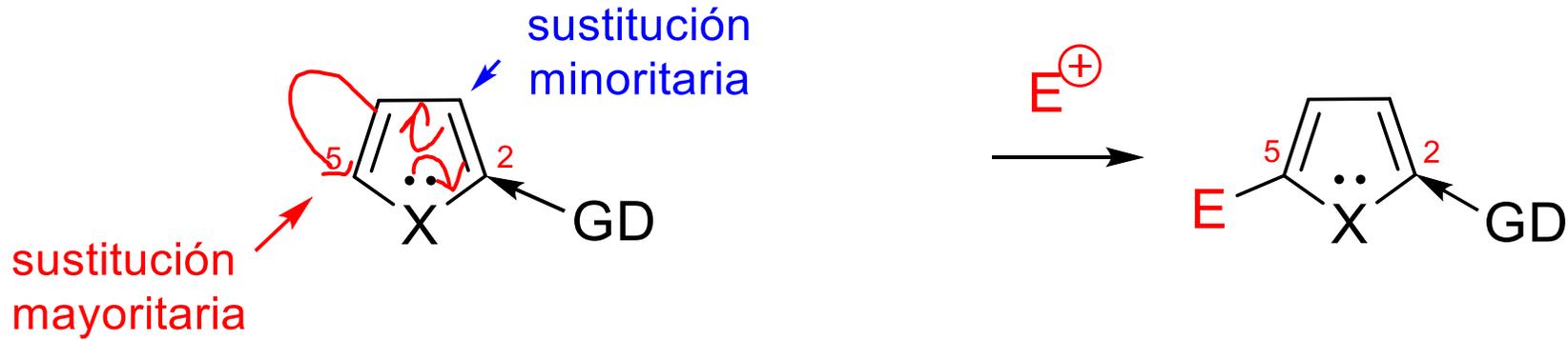
- Donadores de electrones o de densidad electrónica.



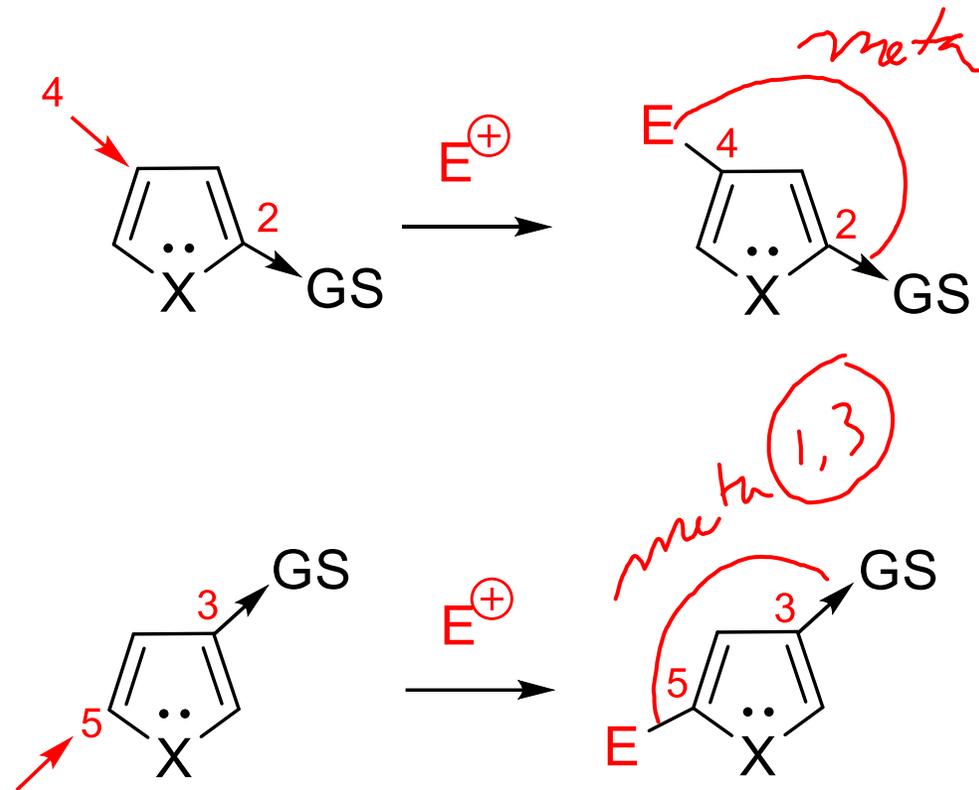
- Sustractores de electrones o de densidad electrónica.



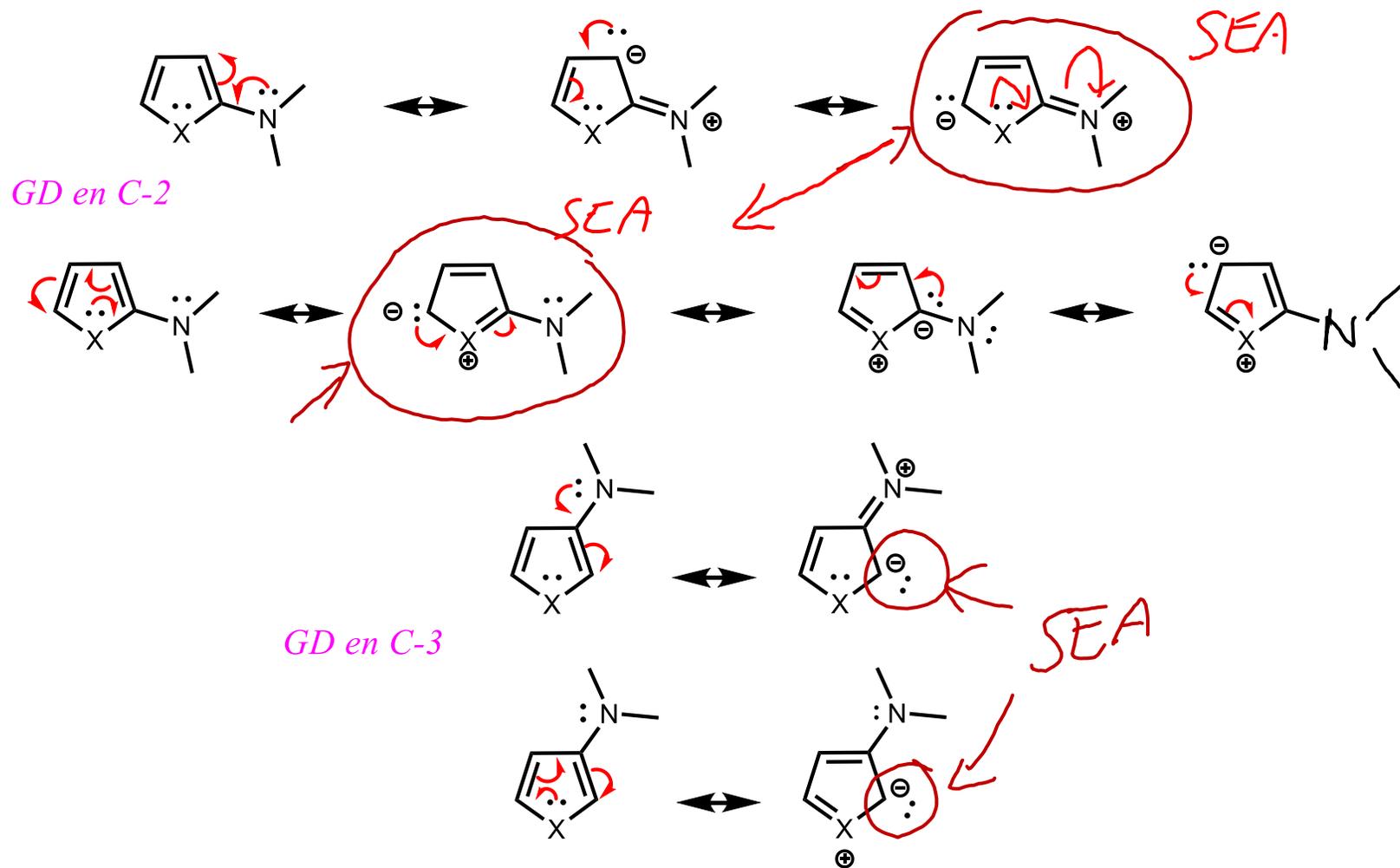
# Sustitución electrofílica en derivados con grupos electrodonadores (GD)



# Sustitución electrofílica cuando hay grupos sustractores de electrones (GS)



# Resonancia y SEA cuando hay un GE



# Resonancia y SEA cuando hay GS

