Compostos Heterocíclicos

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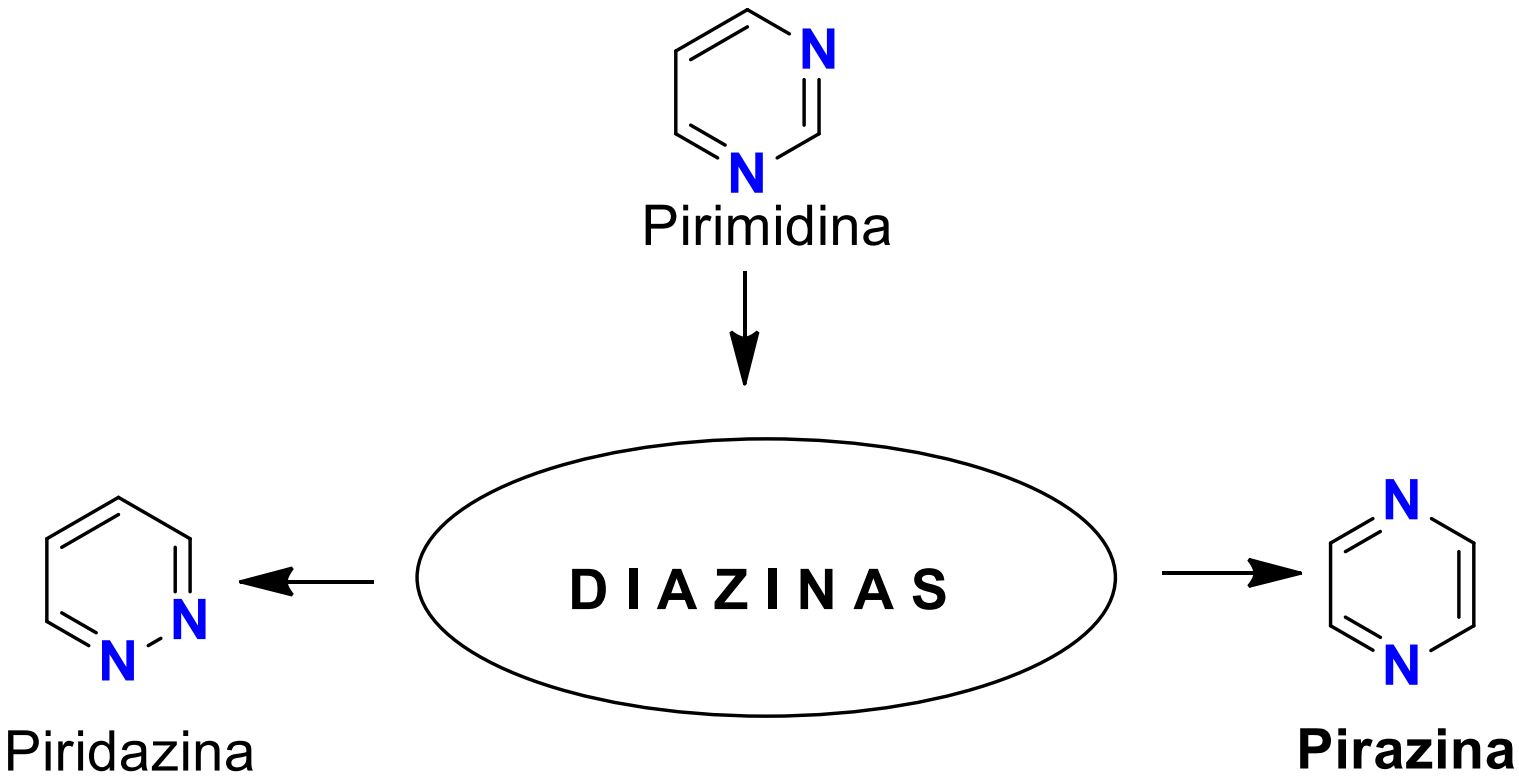
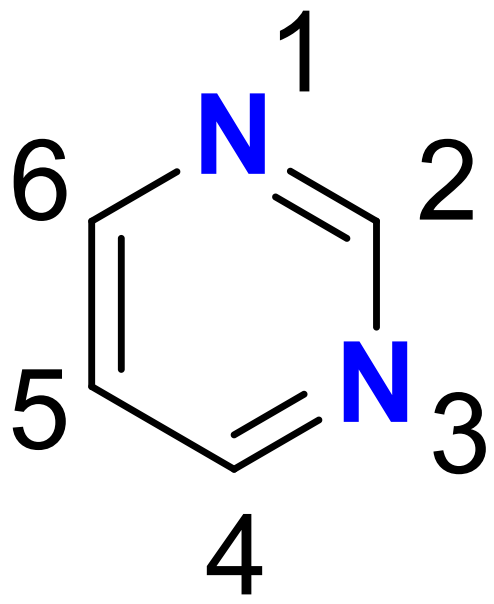
2020

DIAZINAS



Pirimidina

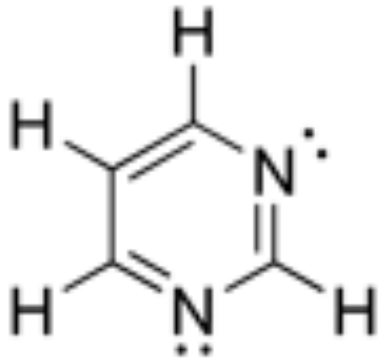
Pirimidina é um composto orgânico aromático similar a piridina. Uma das três **diazinas** (anel heterocíclico de seis membros com dois átomos de nitrogênio), tem os átomos de nitrogênio nas posições 1 e 3 do anel.

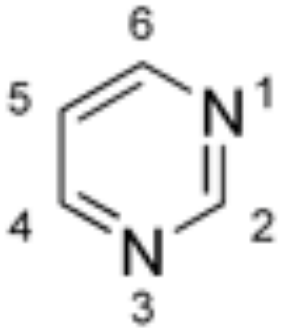


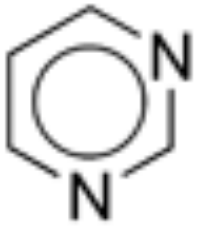
1,3-Diazina

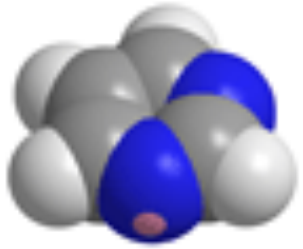
Representação da Pirimidina

As **pirimidinas** são compostos orgânicos semelhantes ao benzeno, mas com um anel heterocíclico: dois átomos de nitrogênio substituem os carbonos nas posições 1 e 3.



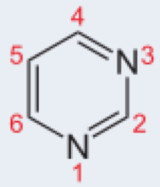




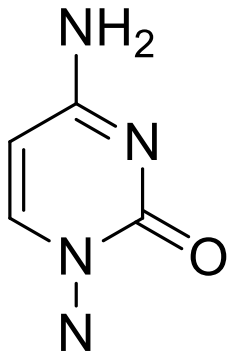


-Fórmula: $C_4H_4N_2$
-Massa molar: 80,088 g/mol
-Ponto de fusão: 20 °C
-Densidade: 1,02 g/cm³
-IUPAC: Pirimidina
-Ponto de ebulição: 123 °C

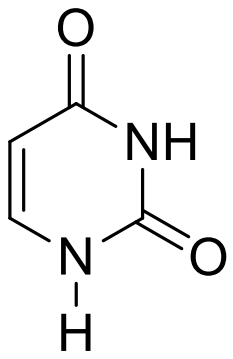
Derivados da pirimidina

Derivados da pirimidina						
Fórmula	Nome	Esquema	R^2	R^4	R^5	R^6
$C_4H_5N_3O$	Citosina		=O	$-NH_2$	–H	–H
$C_4H_4N_2O_2$	Uracil		=O	=O	–H	–H
$C_4H_3FN_2O_2$	Fluorouracil		=O	=O	–F	–H
$C_5H_6N_2O_2$	Timina		=O	=O	$-CH_3$	–H
$C_4H_4N_2O_3$	Ácido barbitúrico		=O	=O	–H	=O
$C_5H_4N_2O_4$	Ácido orótico		=O	–COOH	–H	=O

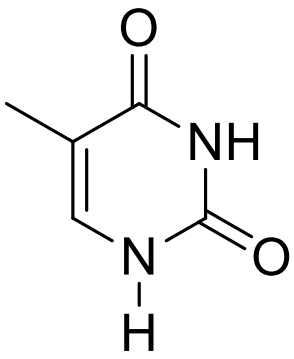
Derivados Pirimidínicos



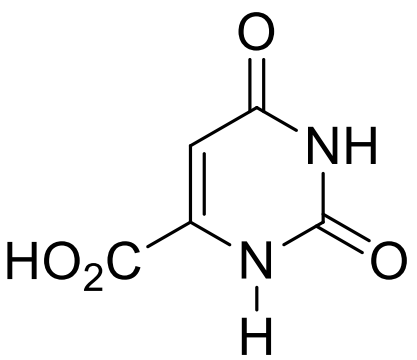
citosina



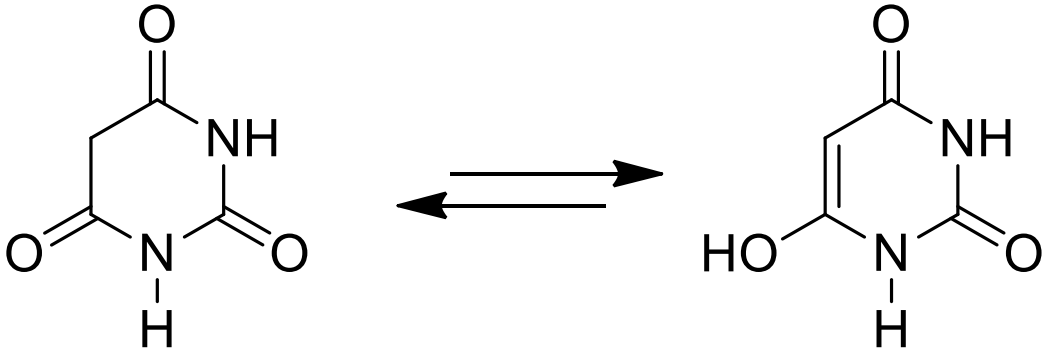
uracila



timina

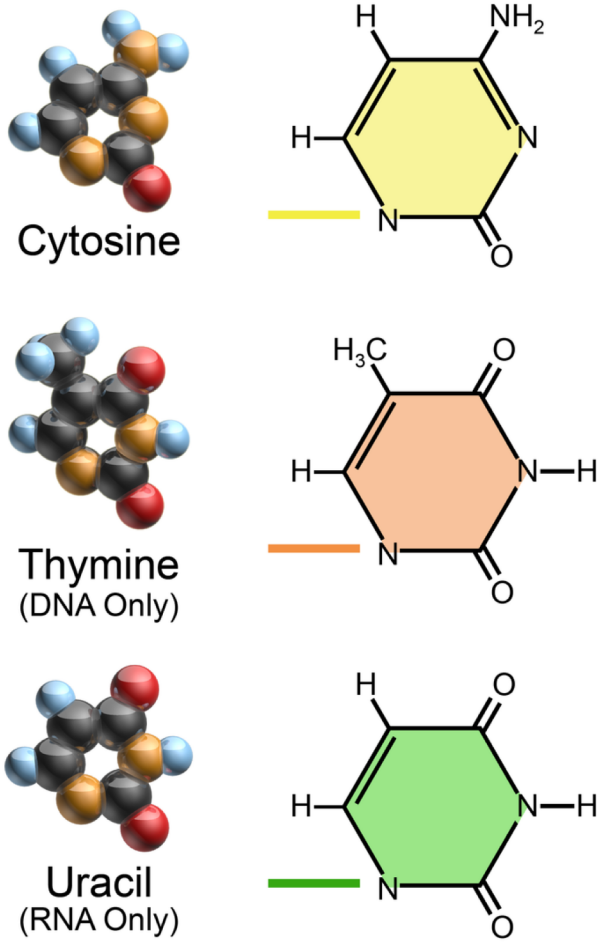


ácido orótico



ácido barbitúrico

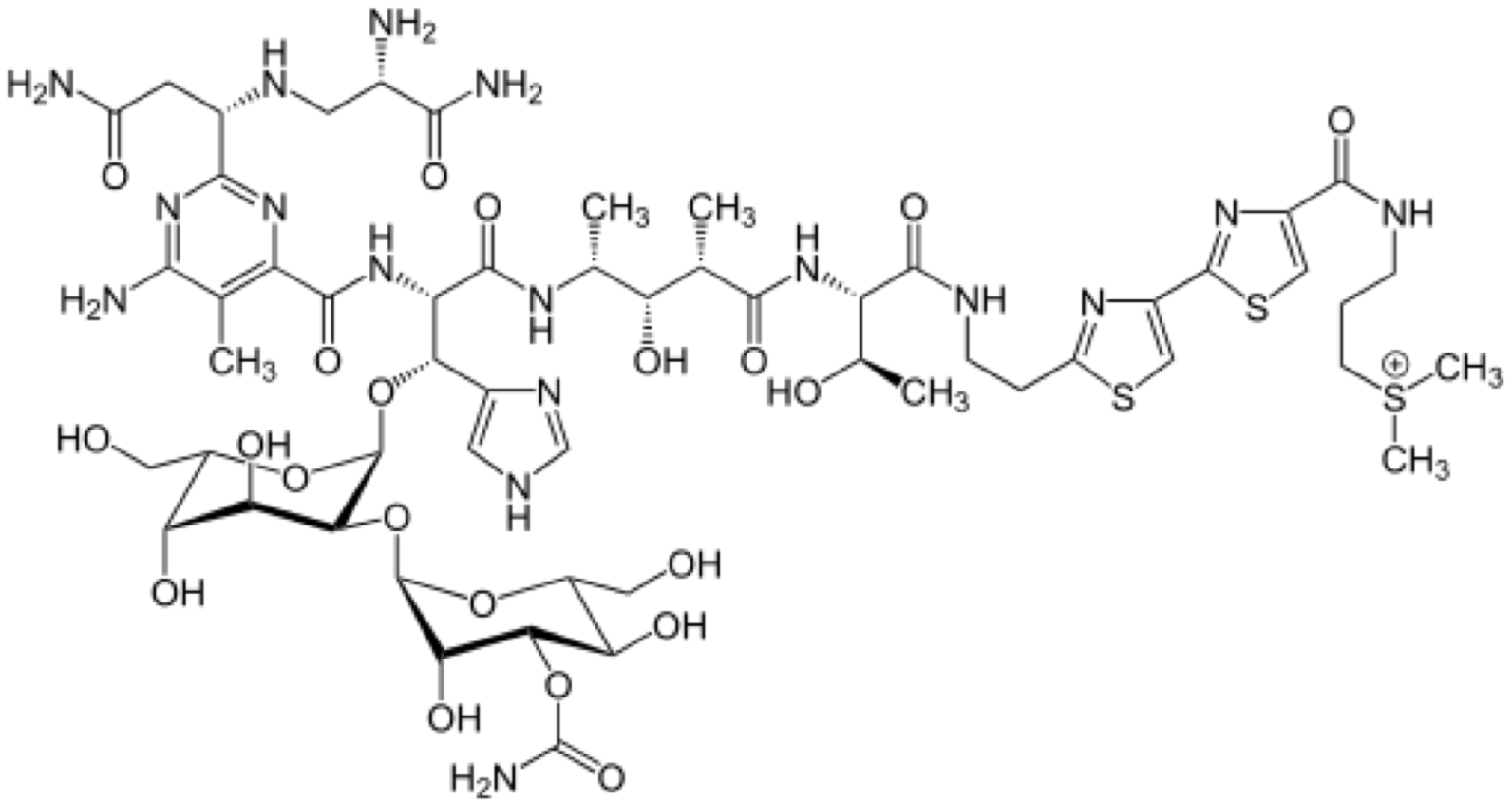
Nucleotídeos



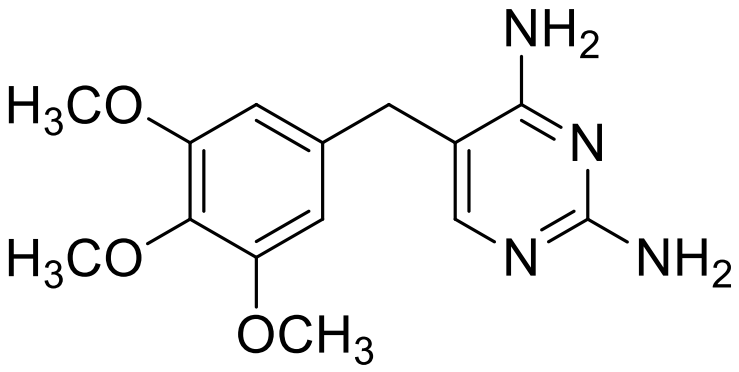
Três bases nucleícas encontradas: citosina (C), timina (T), e uracila (U), são derivados pirimidínicos.

Bleomicina

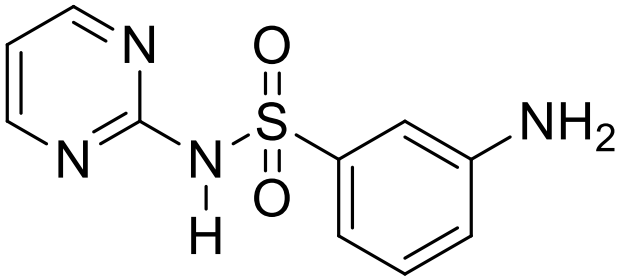
Bleomicina é um fármaco, produto de fermentação de *Streptomyces verticillus*. Indicado normalmente para **neoplasias** de pele, do trato genital e câncer do testículo



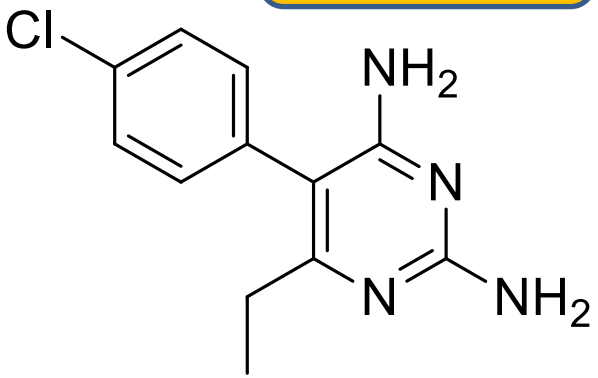
Fármacos



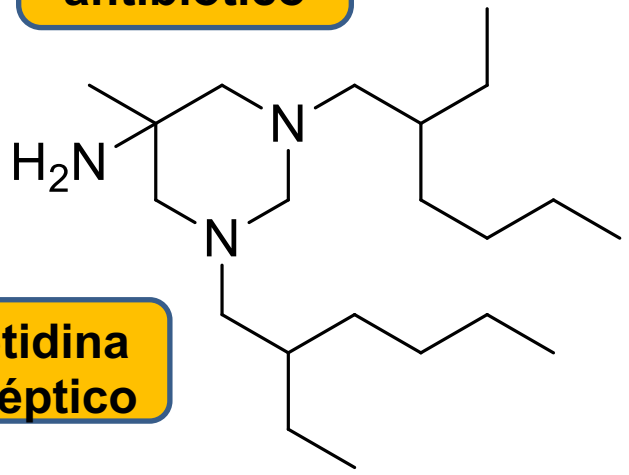
trimetropina
antibiótico



sulfadiazina
antibiótico

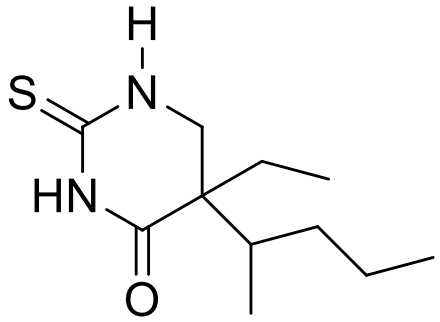


pirimetamina
antiprotozoário

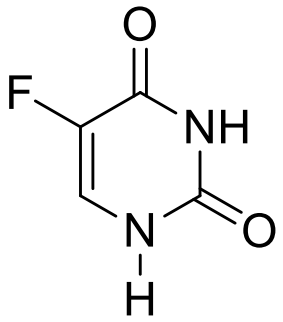


hexetidina
antiséptico

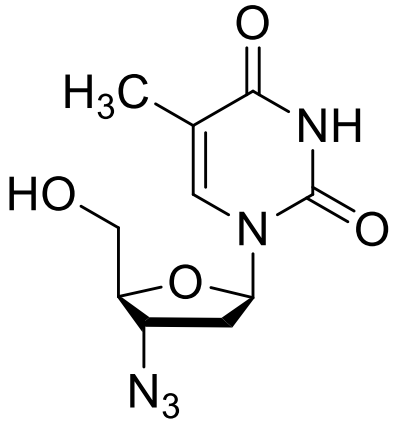
Fármacos



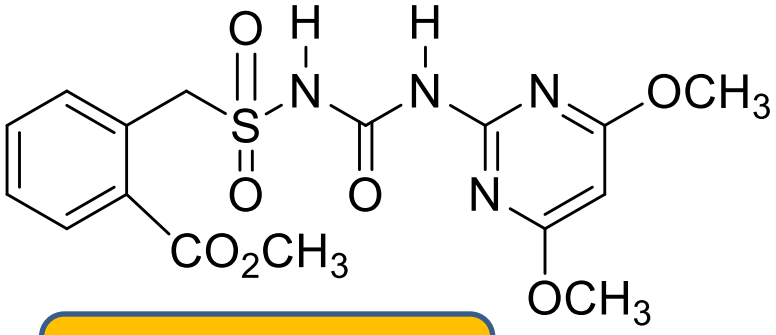
tiopental tiobarbiturato anestésico



fluorouracila anticancerígeno



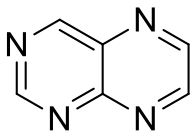
zidovudina retroviral



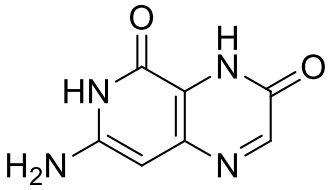
bensulfuron-metil herbicida

Pteridinas

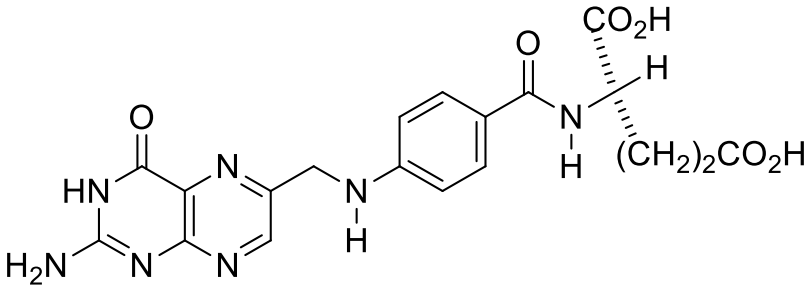
Pirazino[2,3-d]pirimidinas são conhecidas como pteridinas



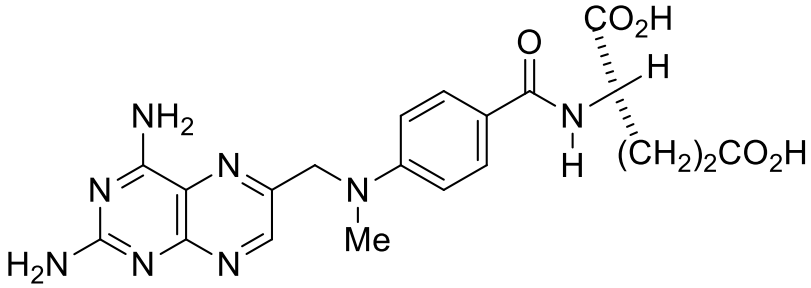
Pteridina



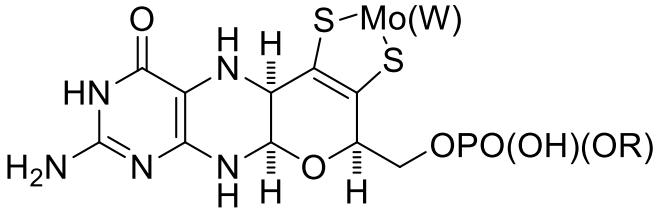
Xantopterina
(Corante amarelo)



Ácido Fólico



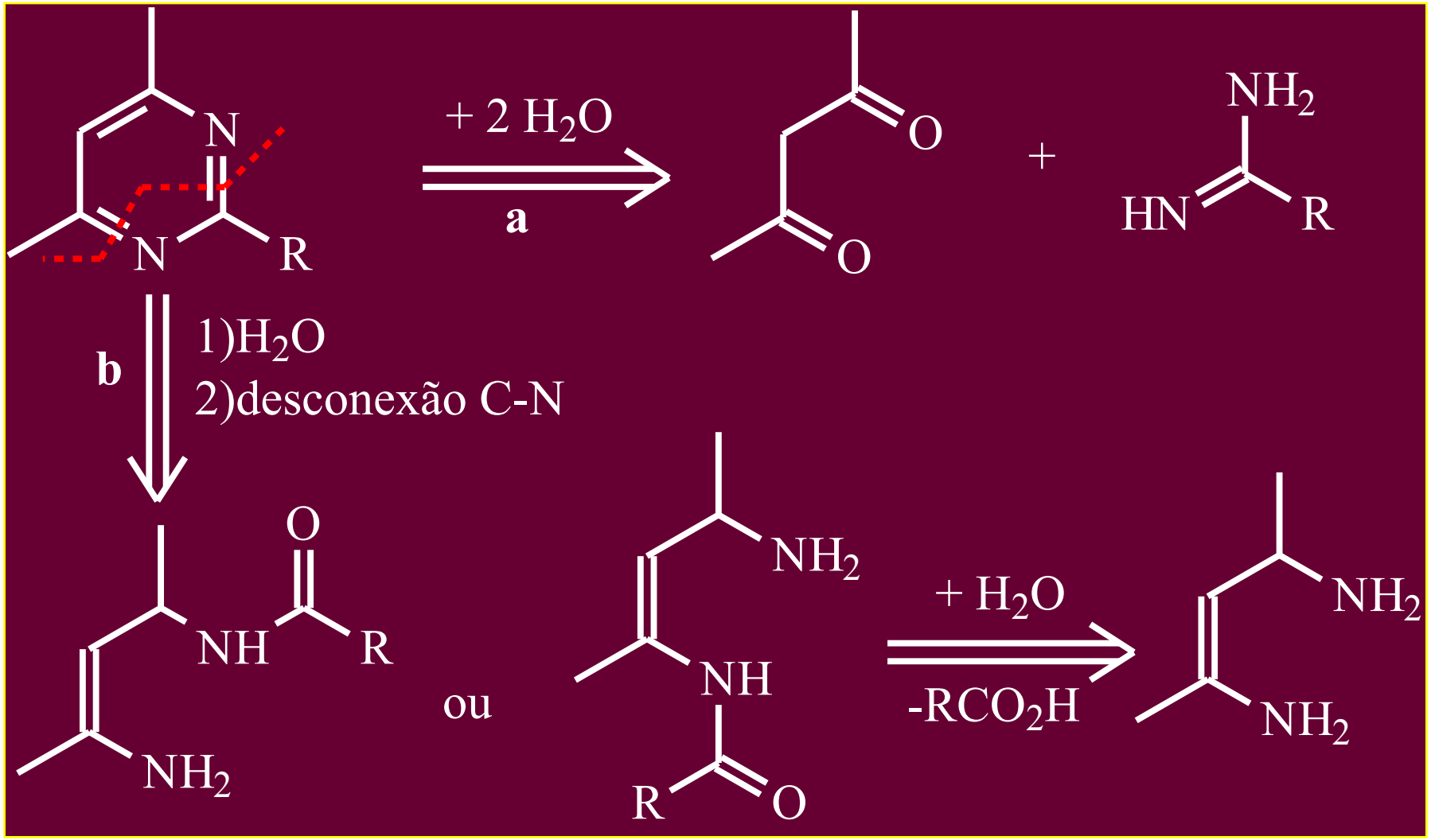
Metotrexato



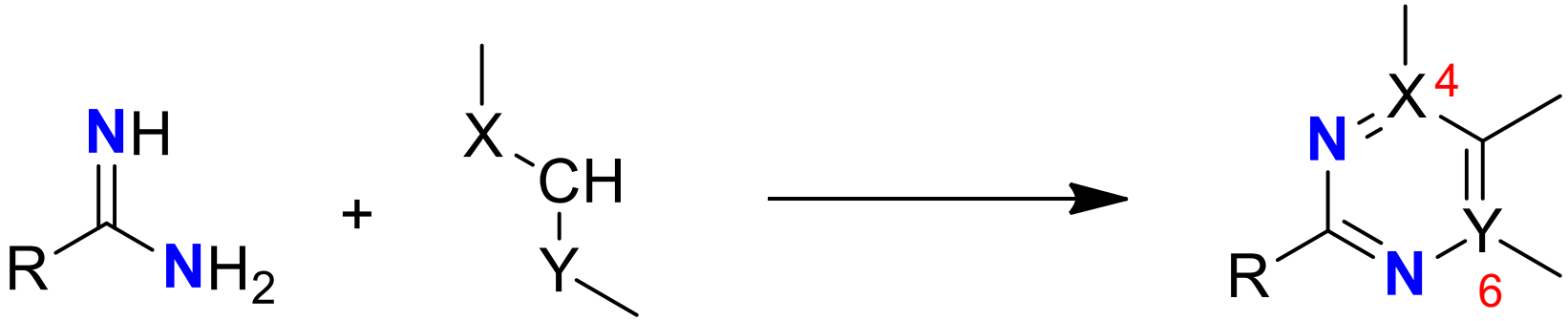
Cofator Molibdênio
(R = H ou nucleosídeo)

Síntese

RETRO-SÍNTESE

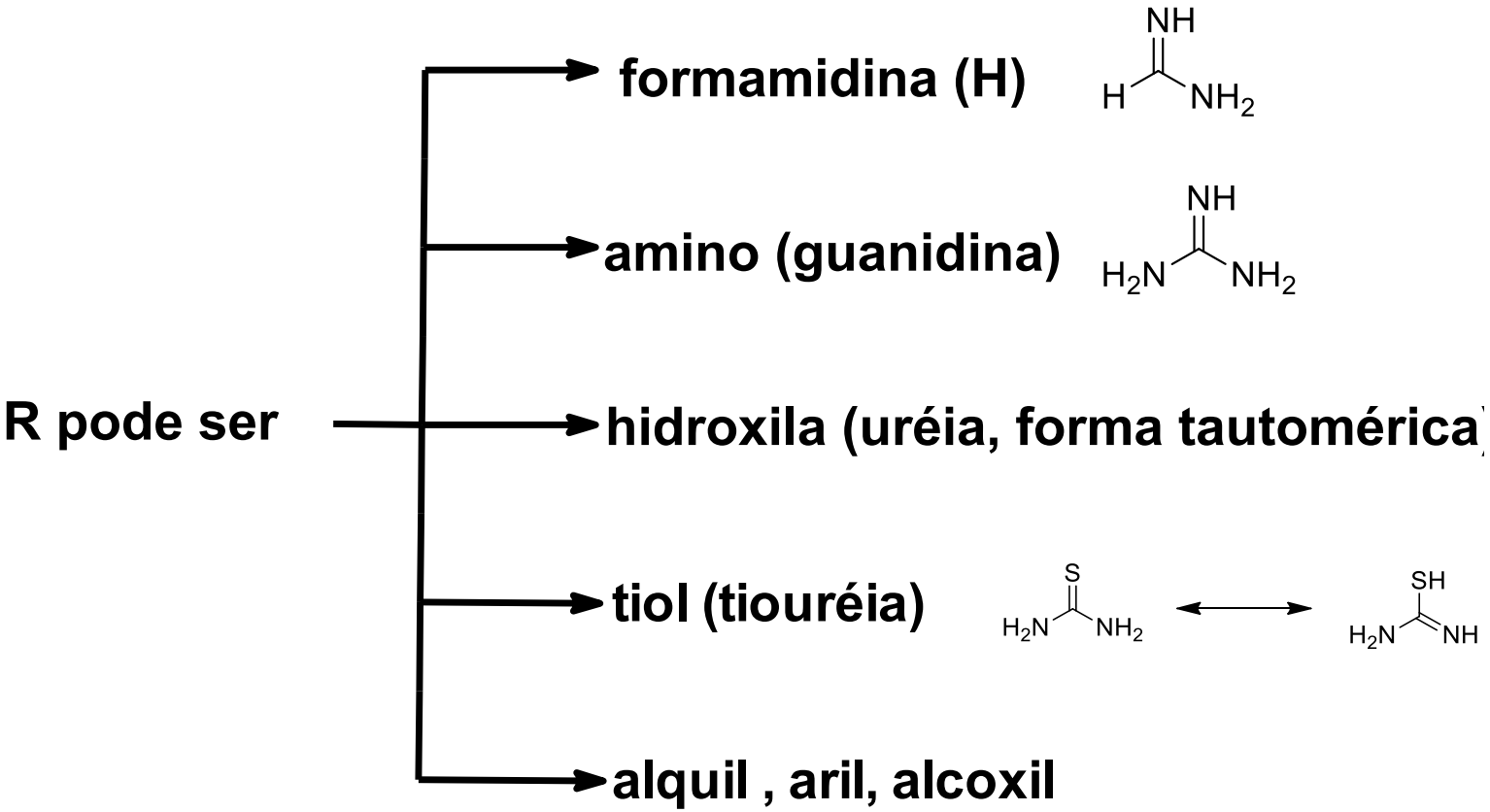


Abordagem Geral: Padrão de Substituição



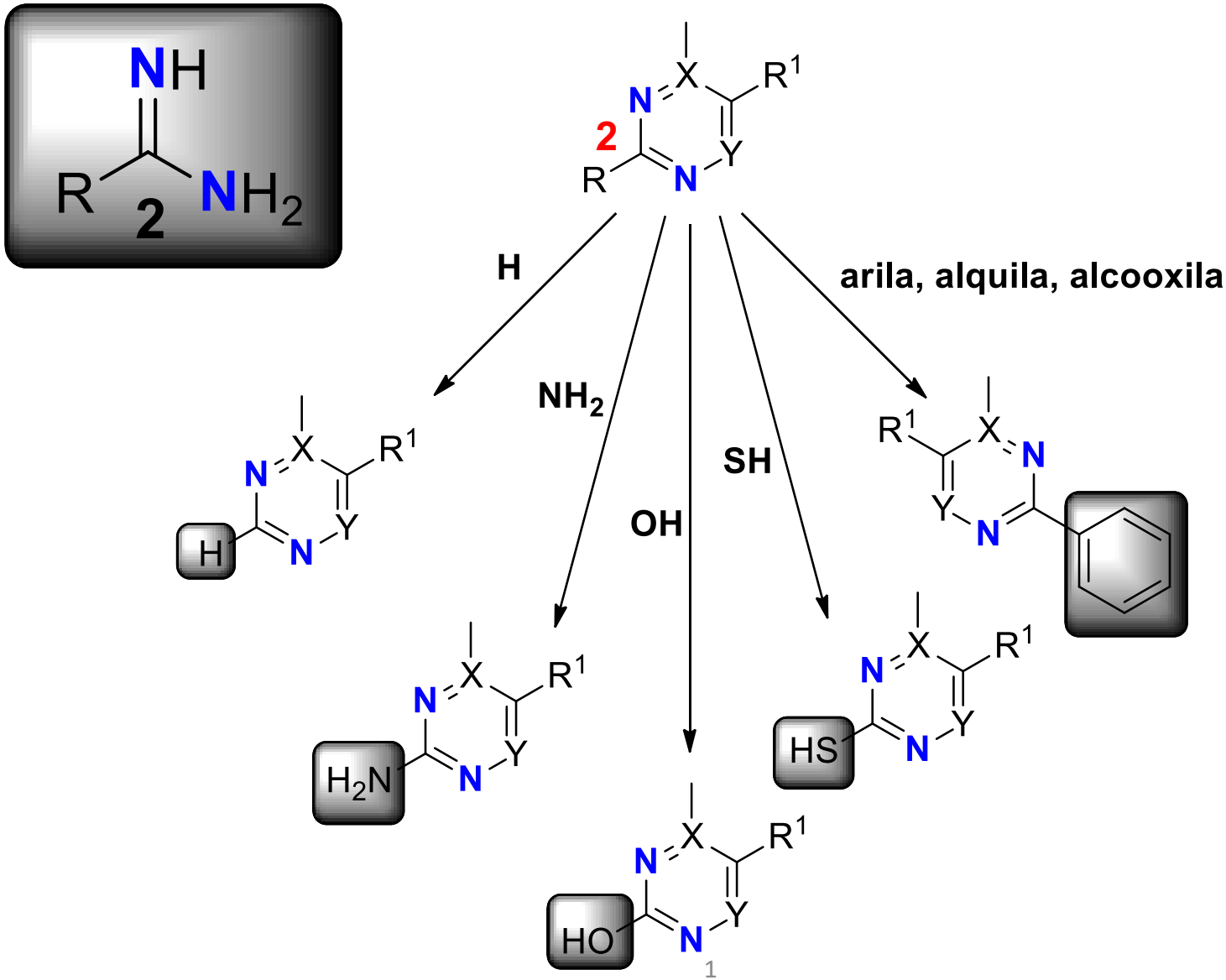
X e Y = Carbonos carbonílicos ou nitrílicos

Sistemas Dinitrogenados

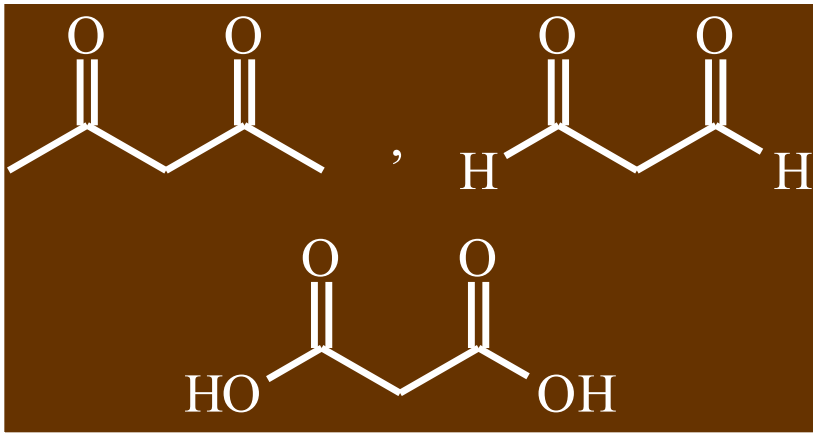


R' determinará a natureza do substituinte na posição 5 (usualmente hidrogênio)

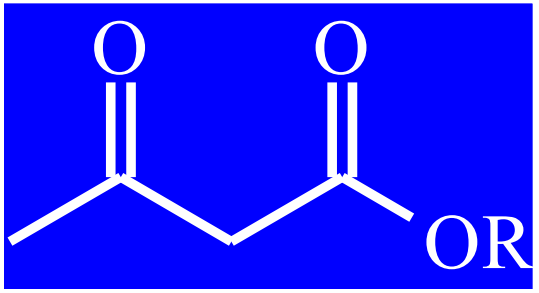
Grupo R (Posição 2)



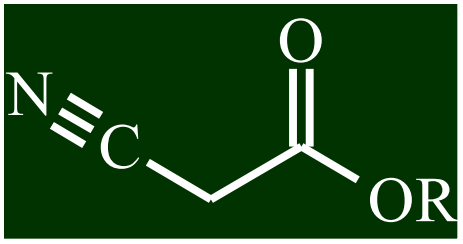
X e Y - Grupos Carbonílicos / Nitrilas



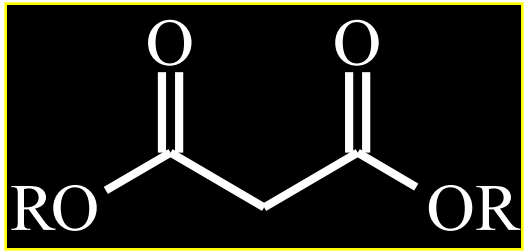
compostos β-dicarbonílcos



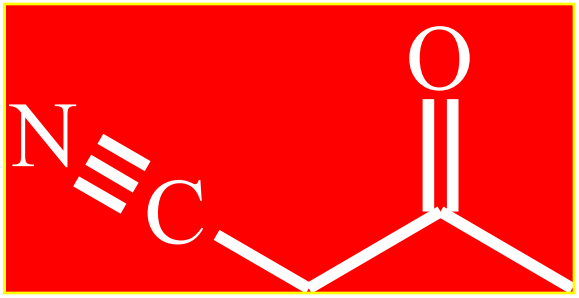
β-ceto éster



α-ciano éster

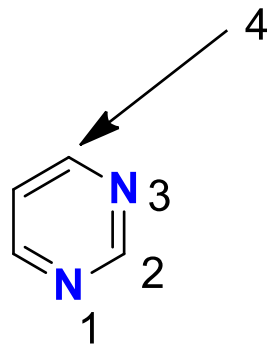


éster malônico



α-ciano cetona

Substituinte : Posição 4

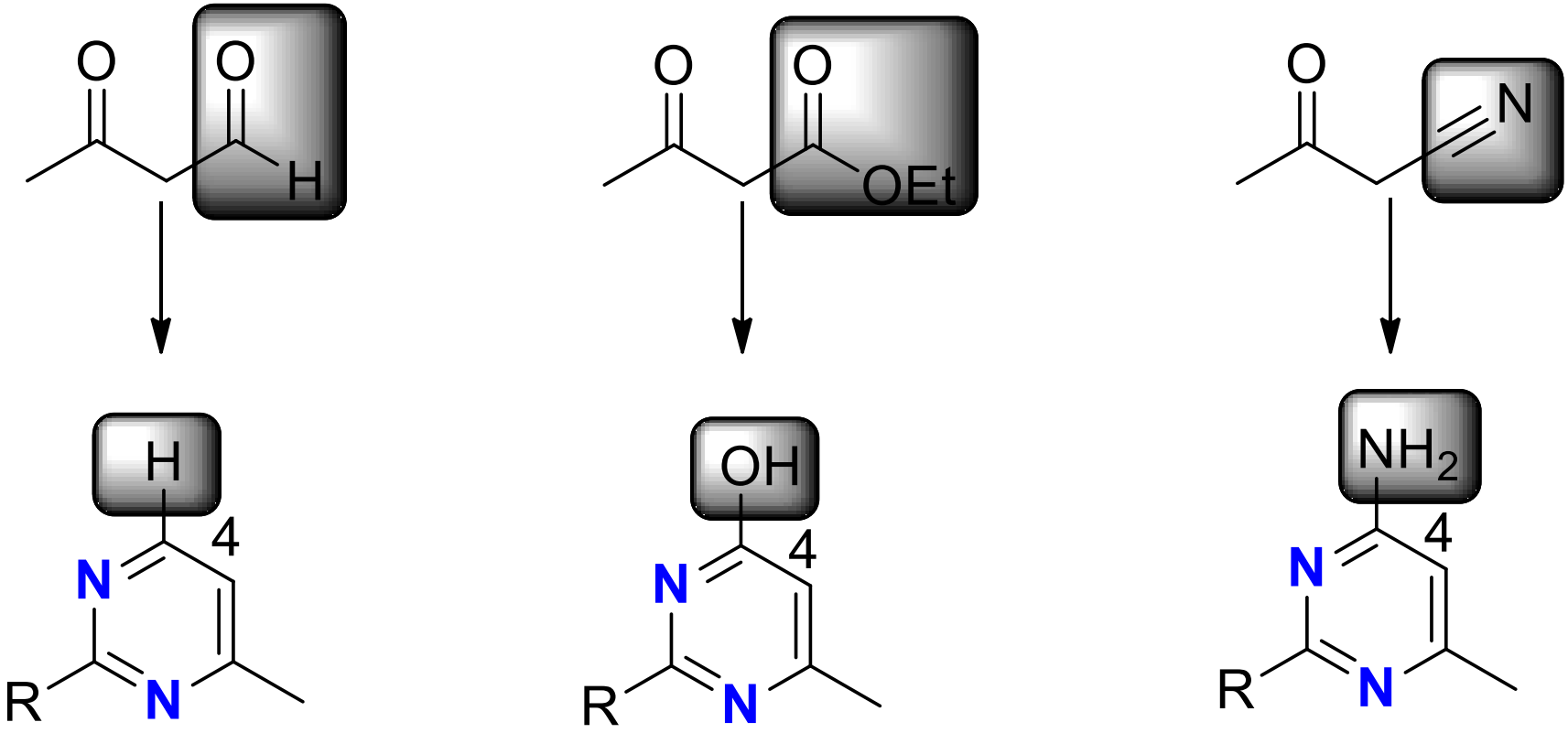


CHO → **A posição 4 não terá substituinte (H)**

CO_2Et → **O substituinte será uma hidroxila (OH)**

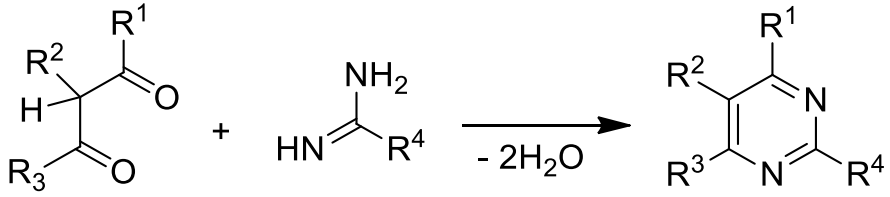
CN → **Forma-se um derivado 4-amino (NH_2)**

SUBSTITUINTE : Posição 4

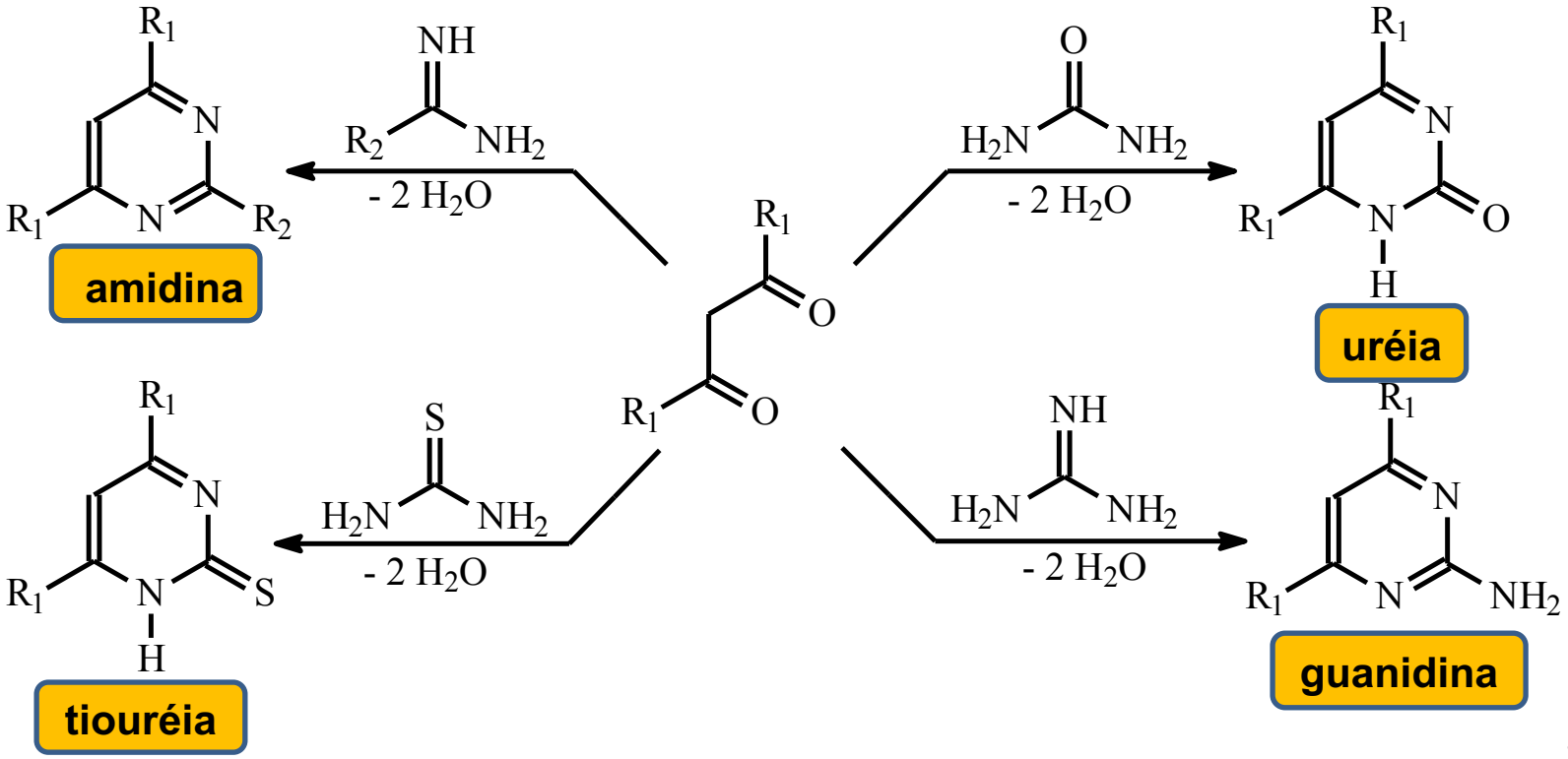


Síntese de Pinner

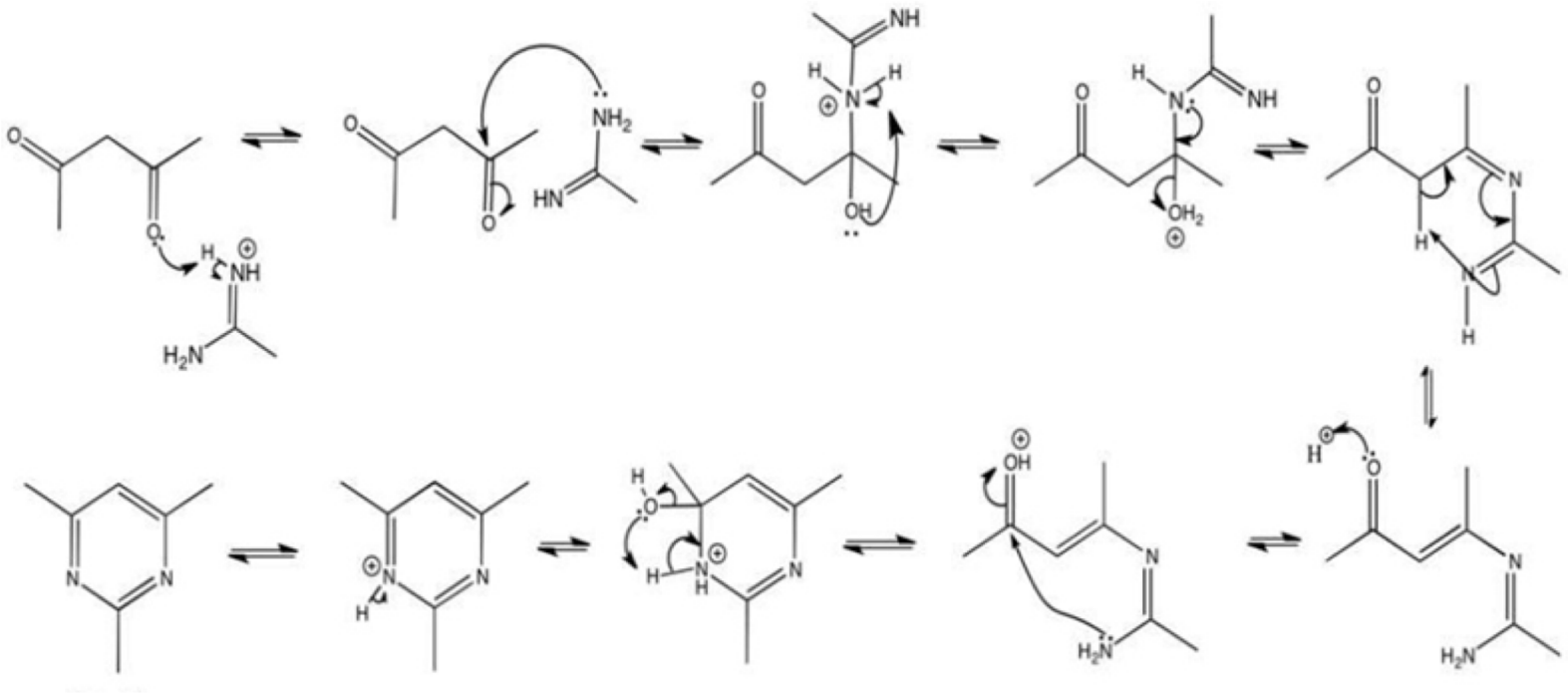
Consiste na reação de condensação de compostos 1,3-dicarbonílicos com amidinas catalisada por ácidos ou bases para formar derivados pirimidínicos.



Exemplos



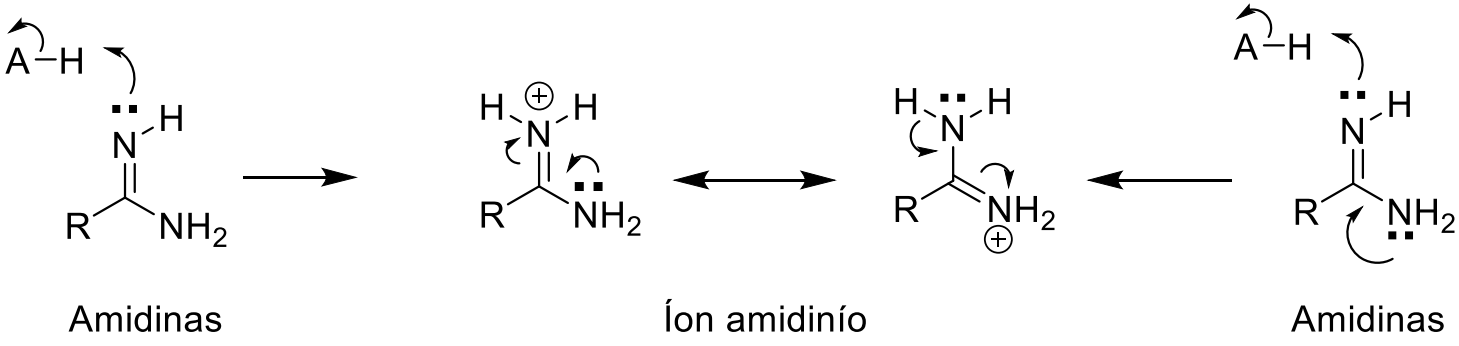
Mecanismo



A condensação de acetilacetona, acetoacetao de metila ou malonato de metila com acetamidina é descrita na referência abaixo.

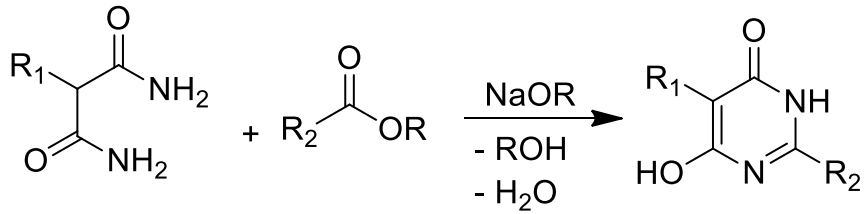
Katritzky, A. R.; Yosaf, T. I. *Can. J. Chem*. **1986**, *64*, 2087

A protonação ocorre no nitrogênio hibridizado na forma sp^2. Isto acontece devido a carga positiva poder ser deslocalizada sobre o outro átomo de nitrogênio. A espécie catiônica resultante é conhecida como íon amidínio.

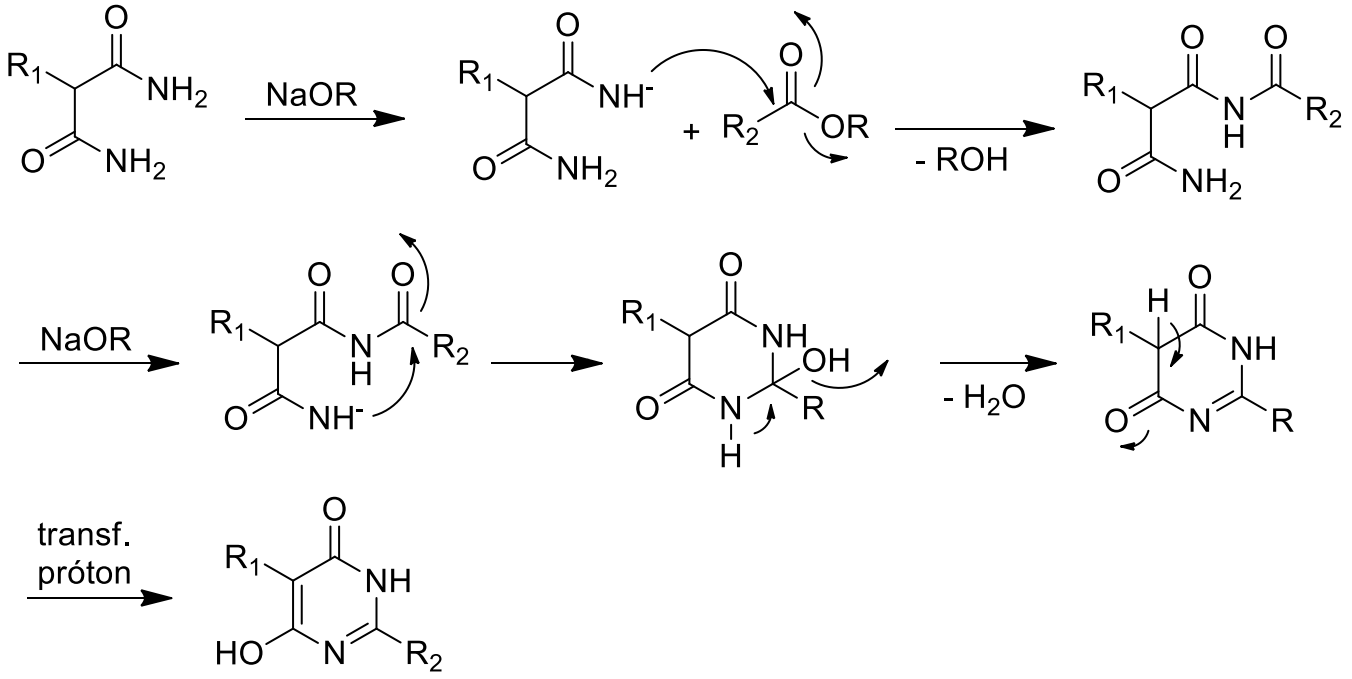


Síntese de Remfry-Hull

A síntese de Remfry-Hull é representada pela condensação de uma α-butilmalondiamida e formato de etil em hidróxido de sódio etanólico para dar 5-butil-6-hidroxipirimidin-4(3H)-ona. A diamida pode ser substituída por uma monotiodiamida e o éster por um cloreto de ácido.

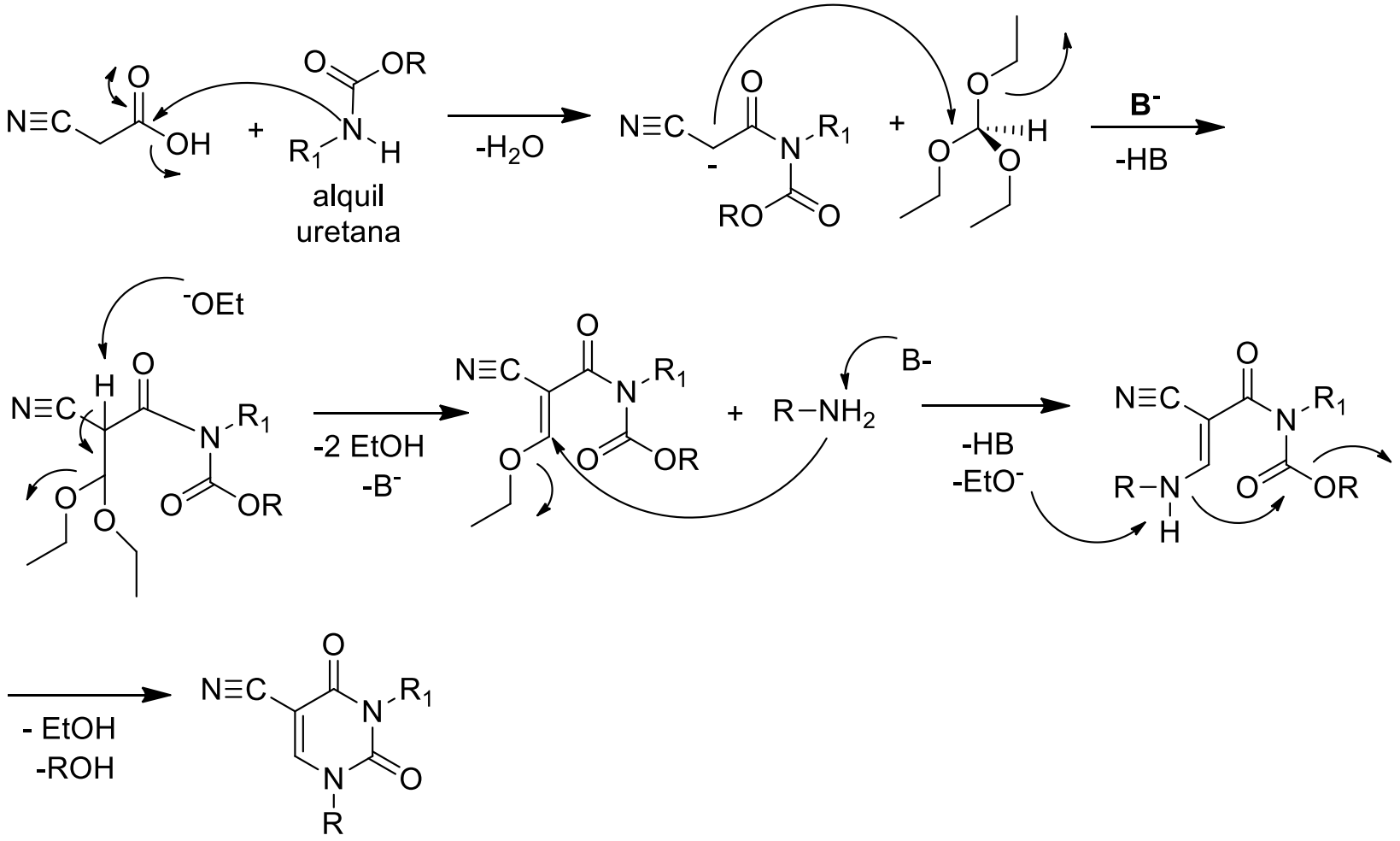


Mecanismo



Síntese de Shaw

Mecanismo

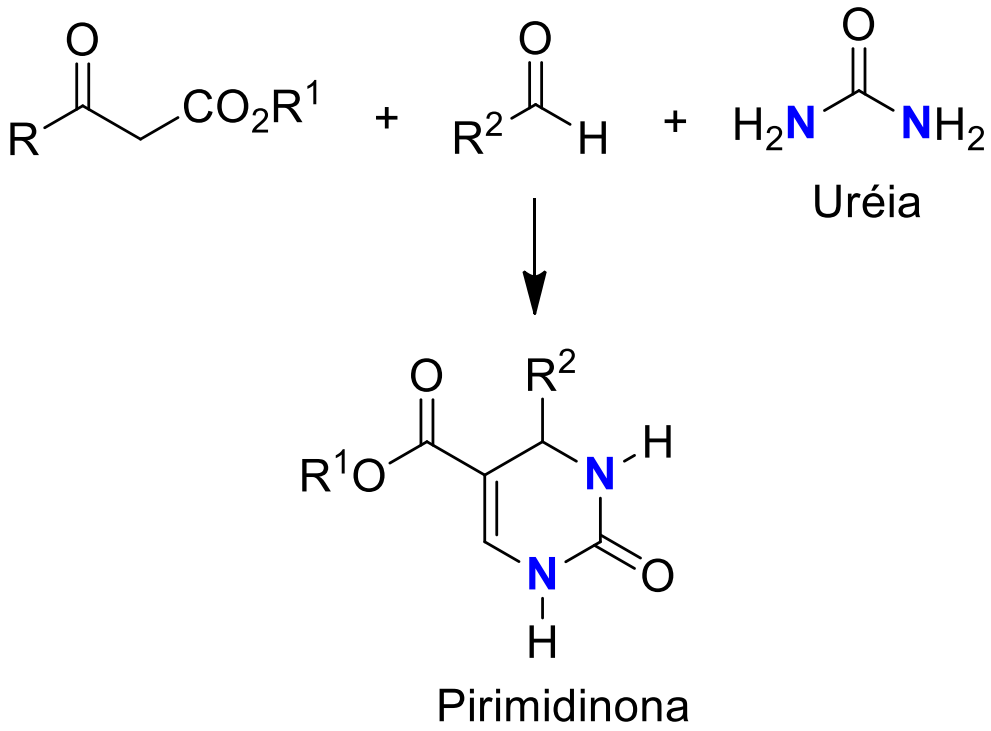


Ortoformiato de etila: $HC(OC_2H_5)_3$

Reação de Biginelli

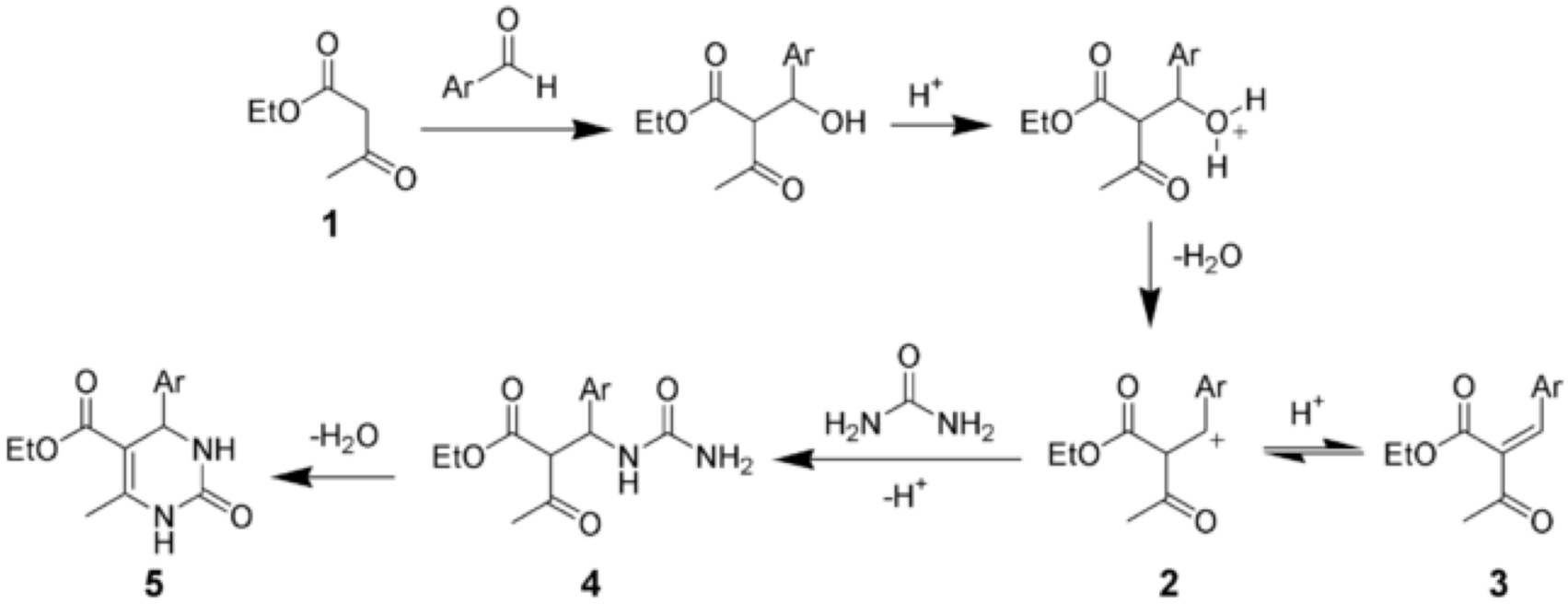
Pietro Biginelli
1860-1937

Reação multicomponente entre um β-cetoéster, aldeído e uréia, catalisada por ácido, gerando 3,4-diidropirimidin-2(1*H*)-onas

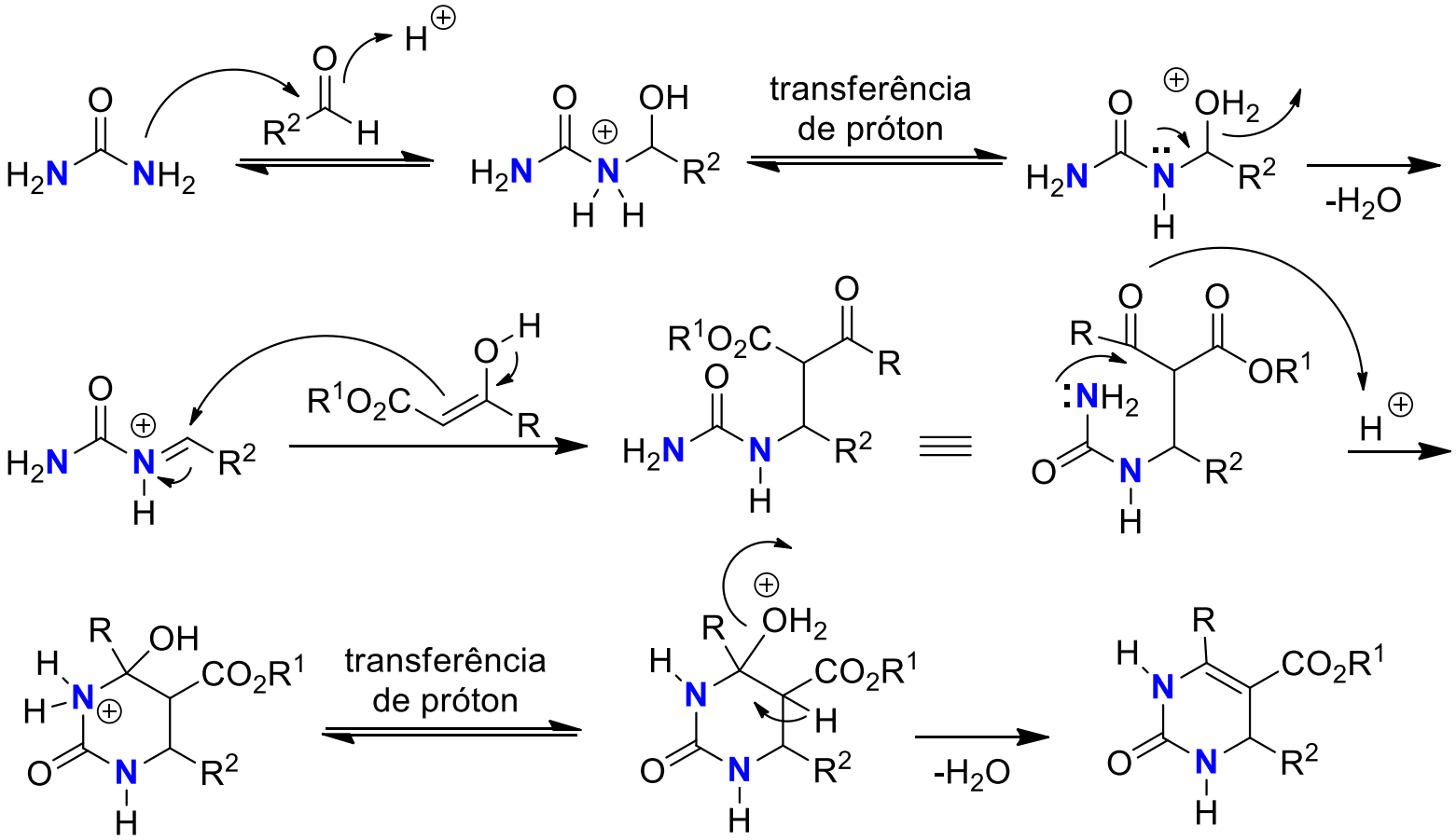


a) Kappe, C. O. *J. Org. Chem*. **1996**, *62*, 7201; b) Hélio A Stefani *Synth. Commun*. **2000**, *30*, 165-173.; c)Jenner, G. *Tetrahedron Lett*. **2004**, *45*, 6195

Reação de Biginelli - Mecanismo



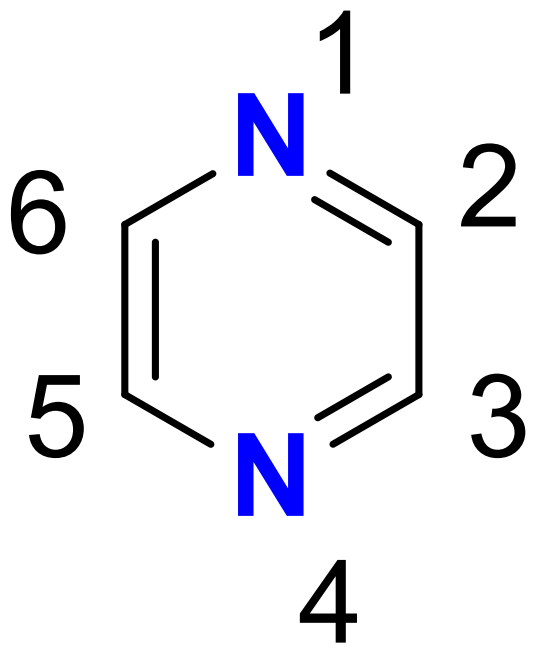
Mecanismo



O mecanismo da reação de Biginelli consiste em uma série de reações bimoleculares que levam a diidropirimidinonas. Condensação aldólica do acetoacetato de etila e o aldeído arílico leva ao íon carbênio. A adição nucleofílica da uréia da o intermediário, o qual rapidamente desidrata para formar o produto.

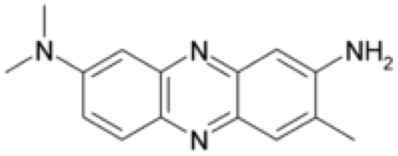
PIRAZINA

Pirazina é um composto heterocíclico aromático com a formula química $C_4H_4N_2$. A pirazina é menos básica que a piridina, piridazina e pirimidina.

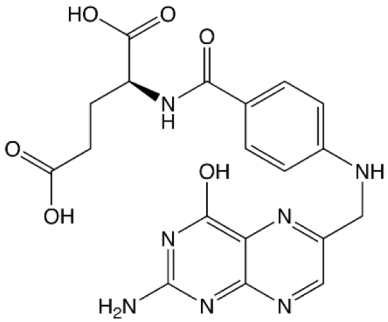


1,4-Diazina

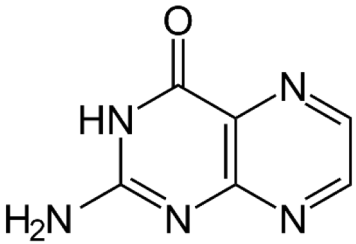
Ocorrências



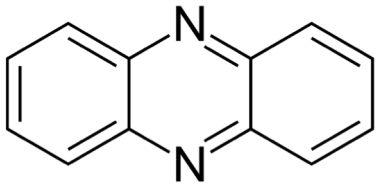
Eurodina
Corante vermelho



Ácido fólico
Vitamina B6

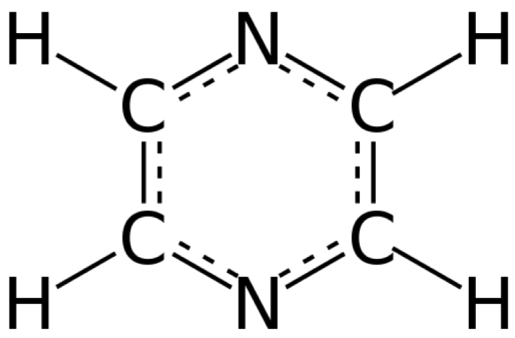


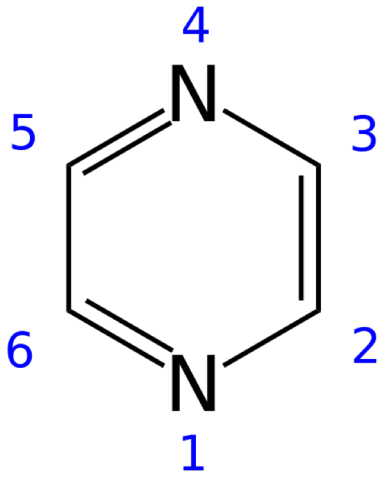
Pterina
Corante

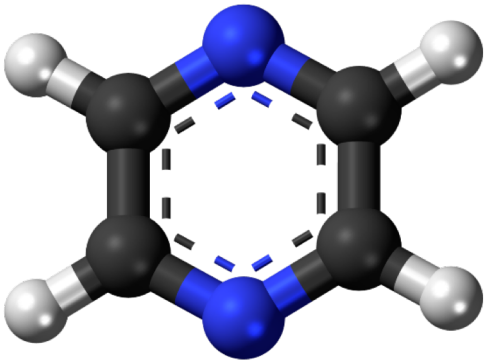


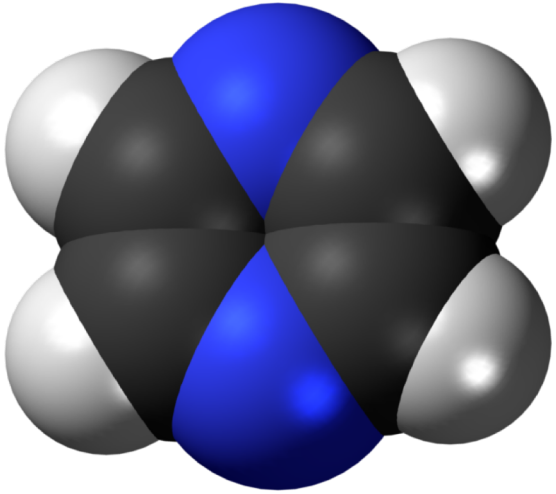
Fenazina
Antitumoral

Representação

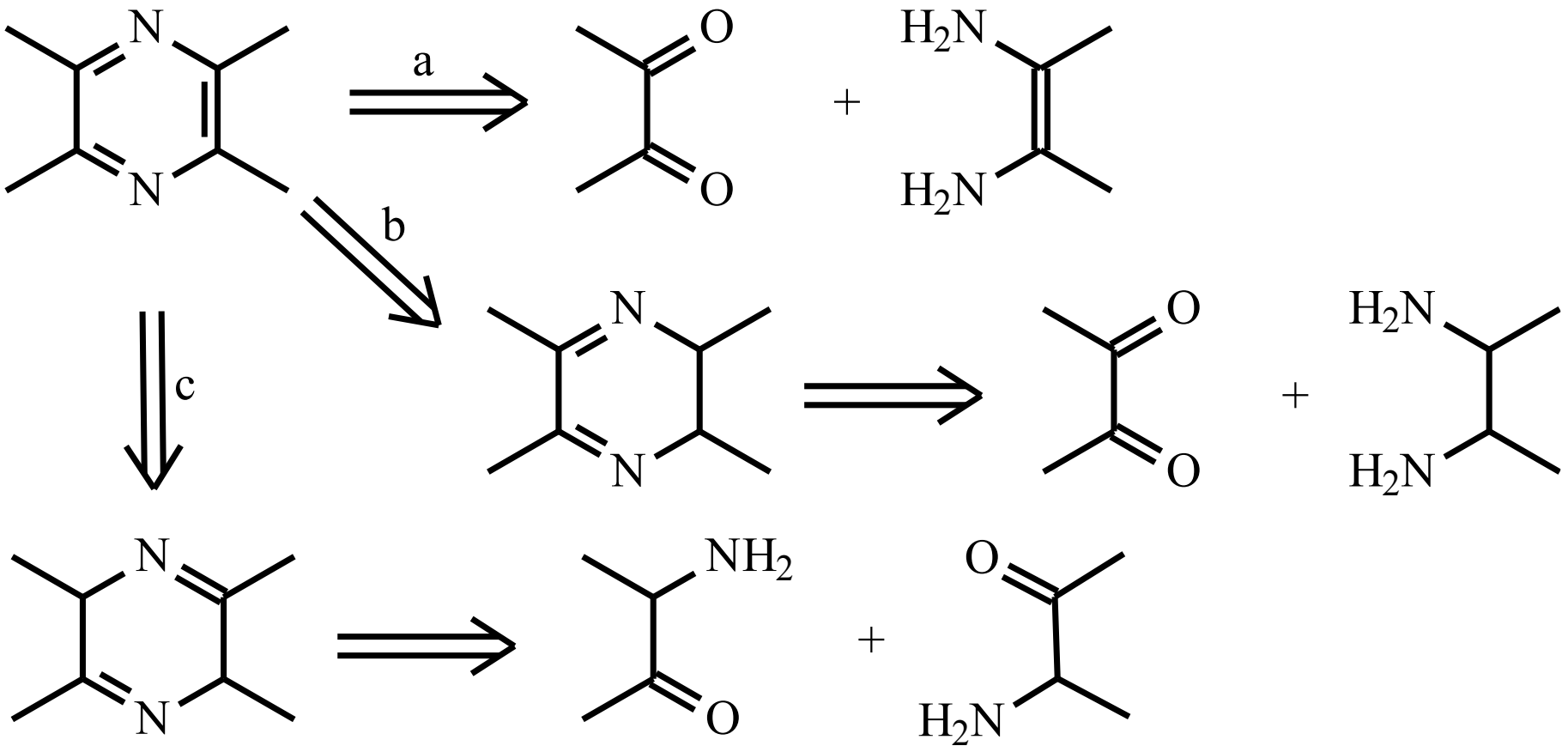




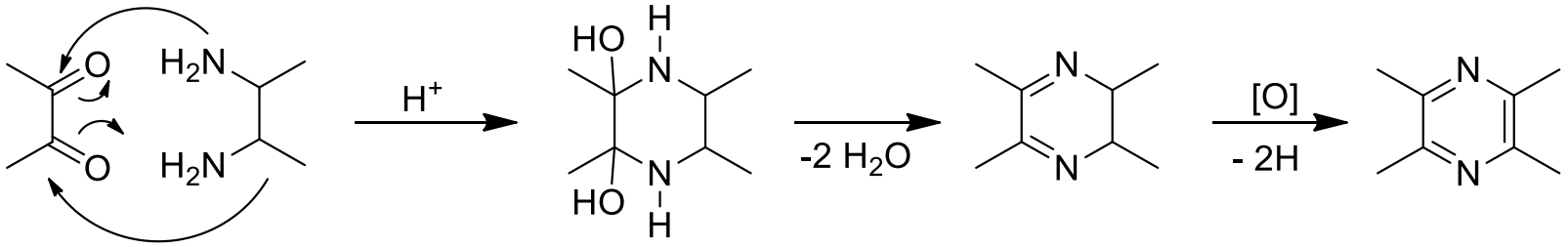




RETRO-SÍNTESE



Ciclocondensação de Compostos 1,2-Dicarbonílicos e 1,2-Diaminoetanos



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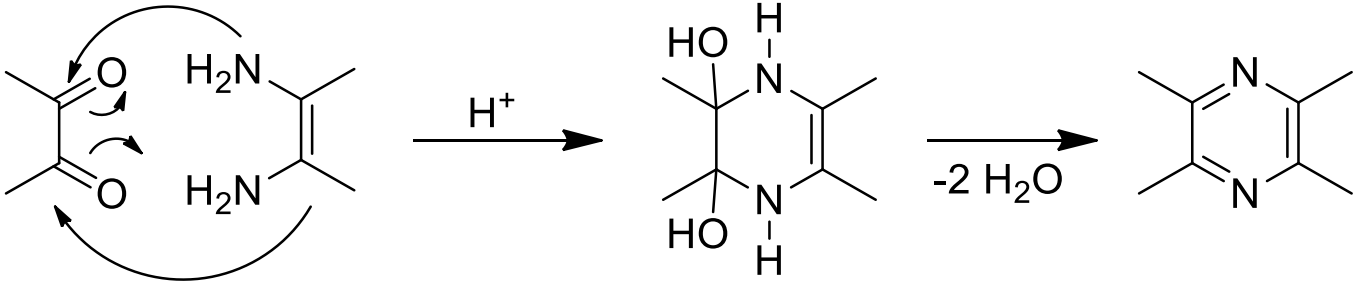
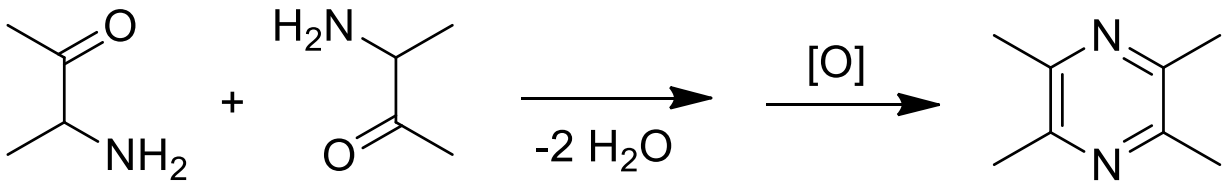
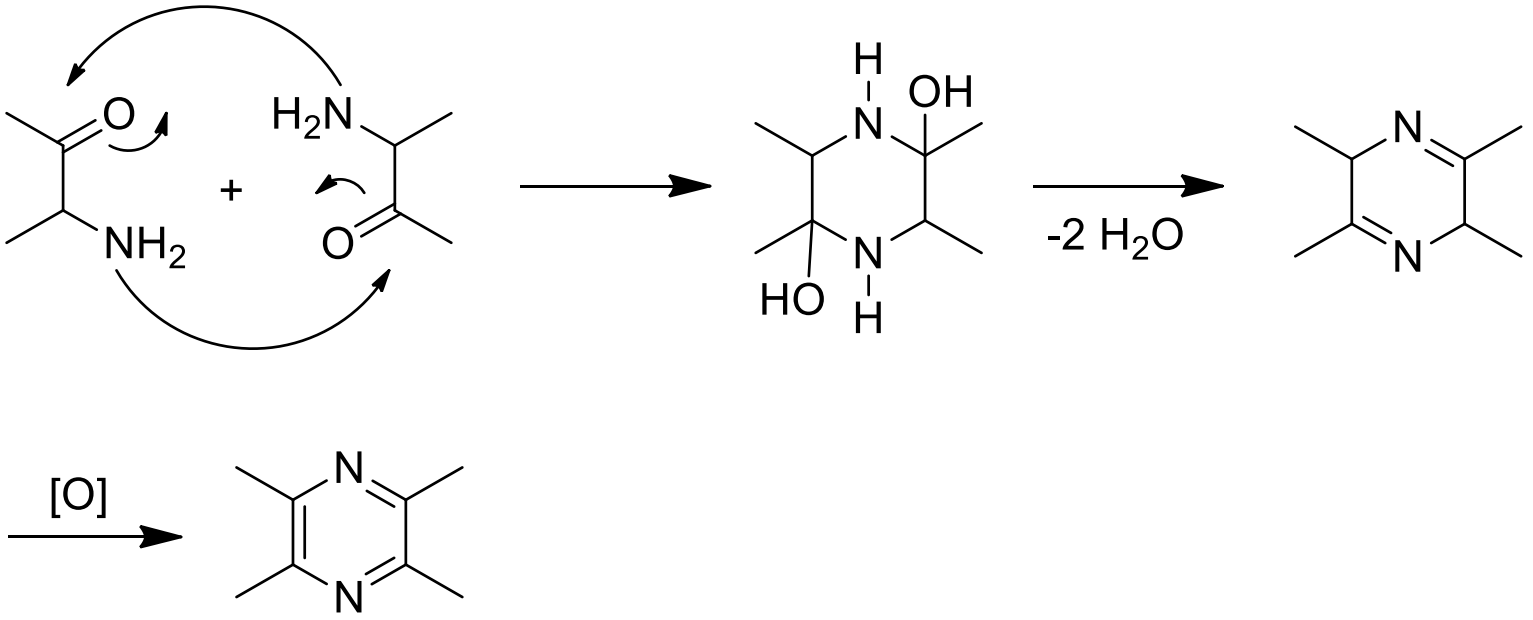


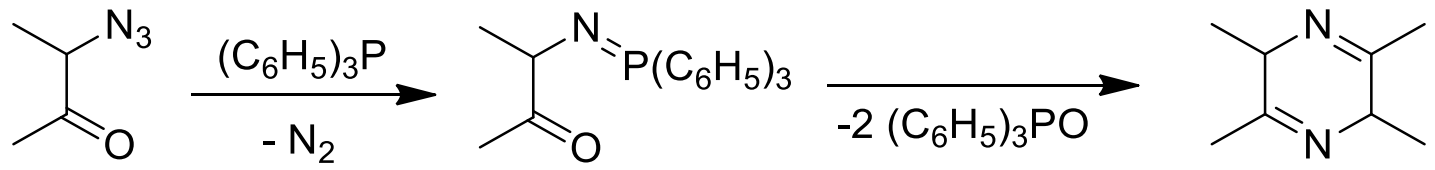
Auto-Condensação de Composto α-AminoCarbonílico - Gutknecht



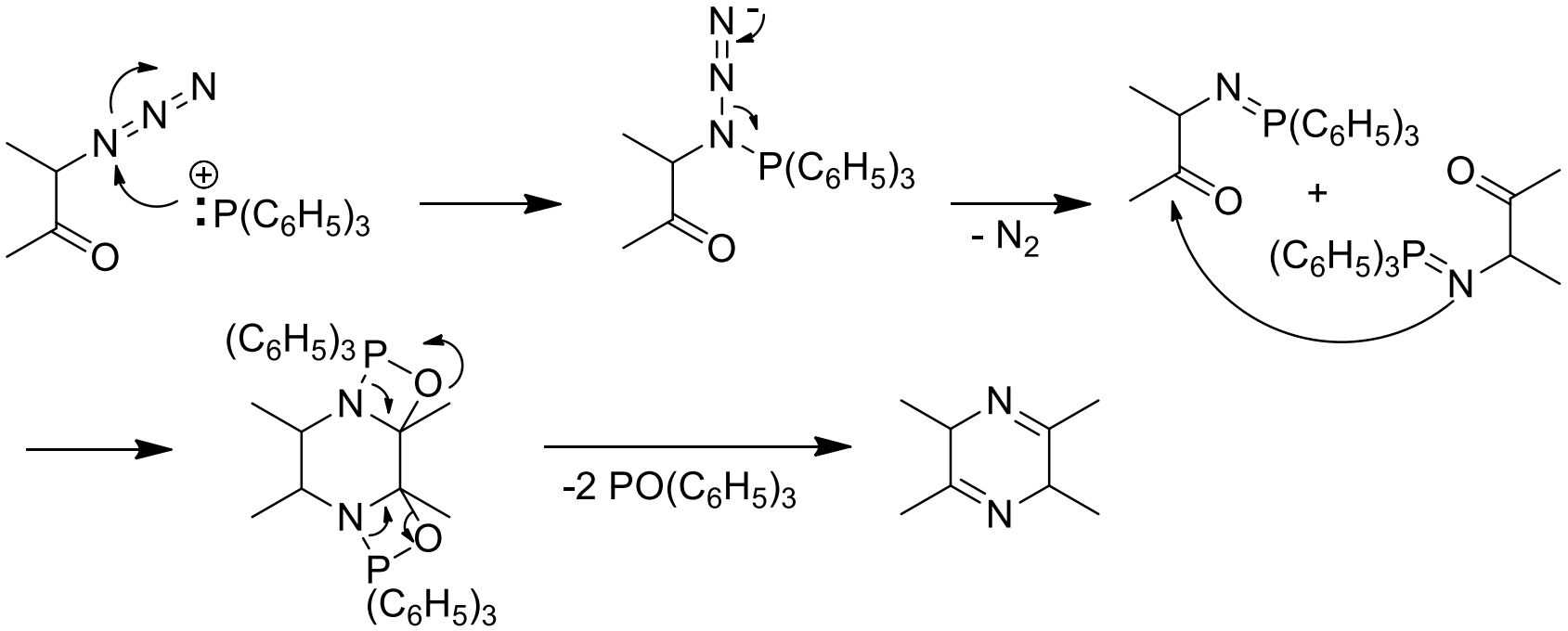
Mecanismo



Reação de Ciclização Aza-Wittig

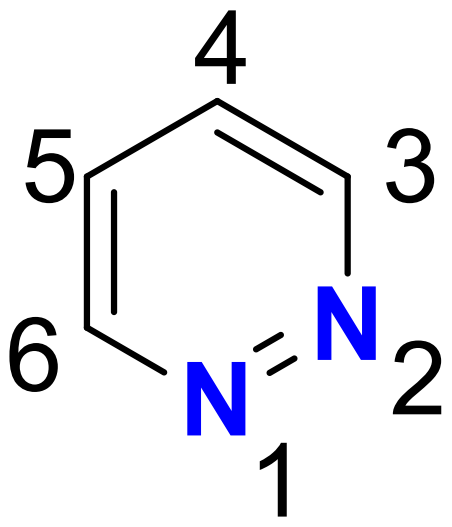


Mecanismo



Piridazina

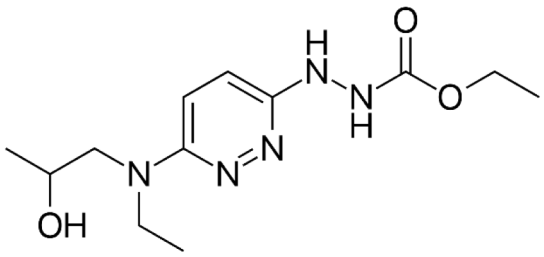
Piridazina é um composto heterocíclico aromático com a fórmula molecular $(CH)_4N_2$. O anel contem seis átomos sendo dois átomos de nitrogênio adjacentes. É um líquido incolor com ponto de ebulição de 208 °C. É isômero de outros dois anéis $(CH)_4N_2$), pirimidina e pirazina.



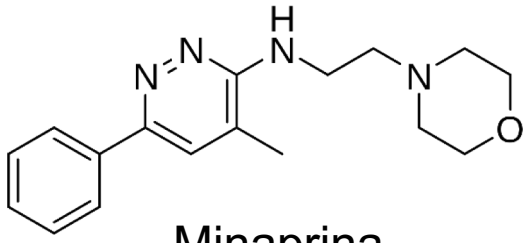
1,2-Diazina

Ocorrência

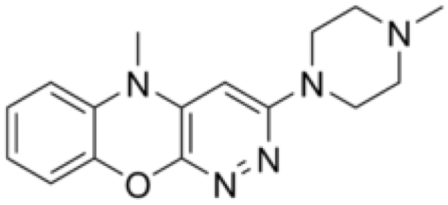
Piridazinas são raras na natureza, possivelmente refletindo a pouca ocorrência de hidrazinas na natureza, é um "bloco de construção" comum para a síntese destes heterociclos. A estrutura da piridazina é um farmacofóro popular encontrado em inúmeros herbicidas tais como credazina, piridafol e piridato. É também encontrado na estrutura de vários compostos tais como cefozopran, cadralazina, minaprina, pipofezina, hidralazina, e cilazapril.



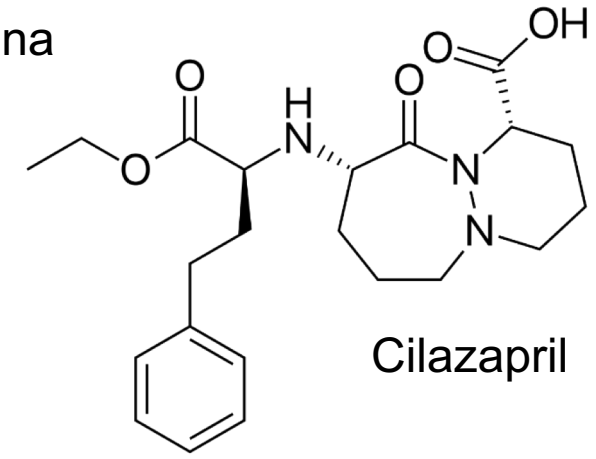
Cadralazina



Minaprina

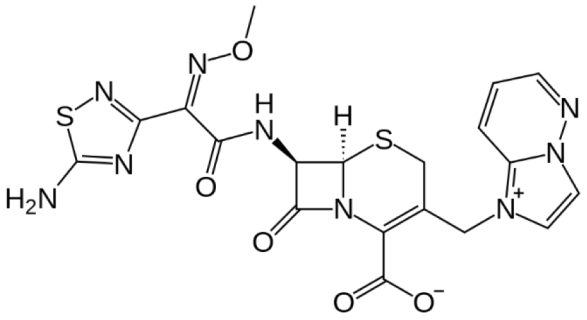


Pipofezina

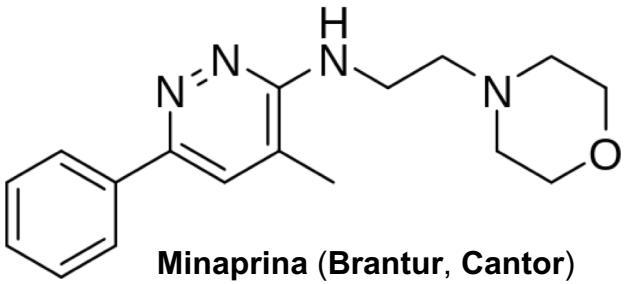


Cilazapril

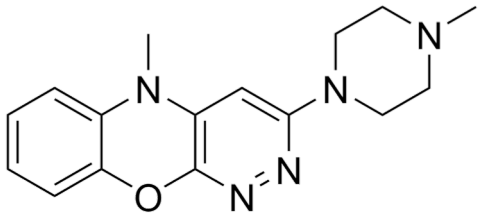
Farmácos



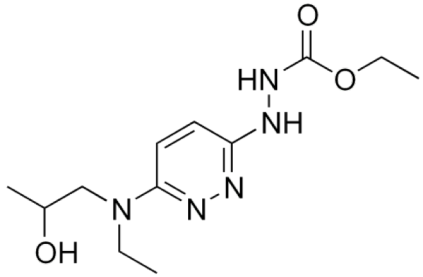
Cefozopran (INN) is a fourth-generation cephalosporin



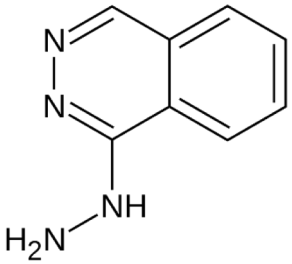
Minaprina (**Brantur**, **Cantor**) is an antidepressant



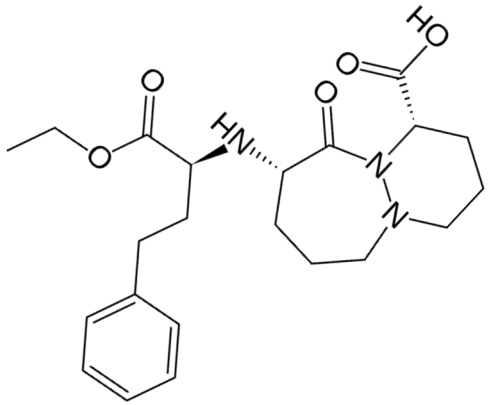
Pipofezina (**Azafen** or **Azaphen**) is a tricyclic antidepressant (TCA)



Cadralazina is an antihypertensive of the hydrazinophthalazine chemical class

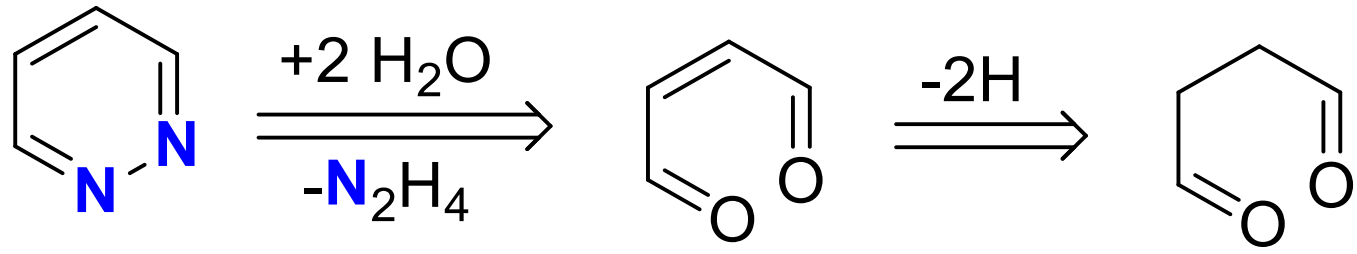


Hydralazina (**Apresoline**) is a direct-acting smooth muscle relaxant used to treat hypertension



Cilazapril is an angiotensin-converting enzyme inhibitor (ACE inhibitor) used for the treatment of hypertension and congestive heart failure

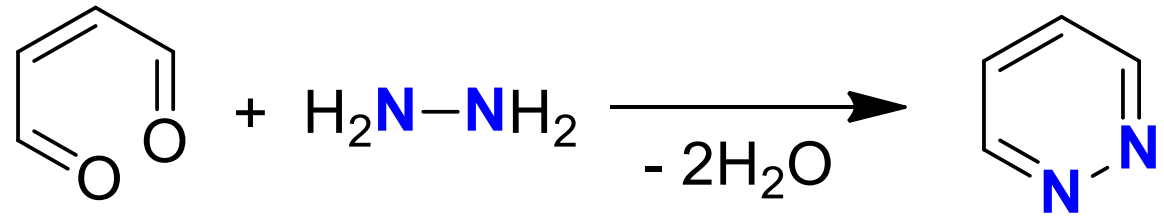
Retro-Síntese



Piridazina

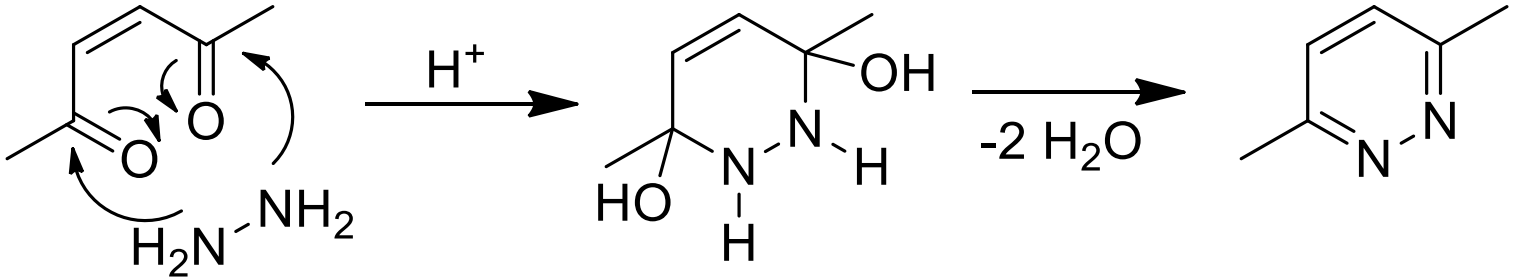
Composto 1,4- Dicarbonílico

Ciclocondensação de Compostos 1,4-Dicarbonílicos α,β-Insaturados com Hidrazina

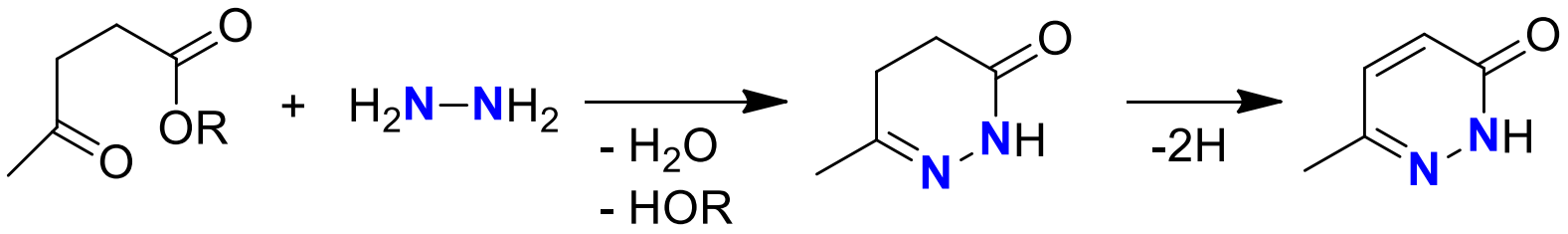


Piridazina

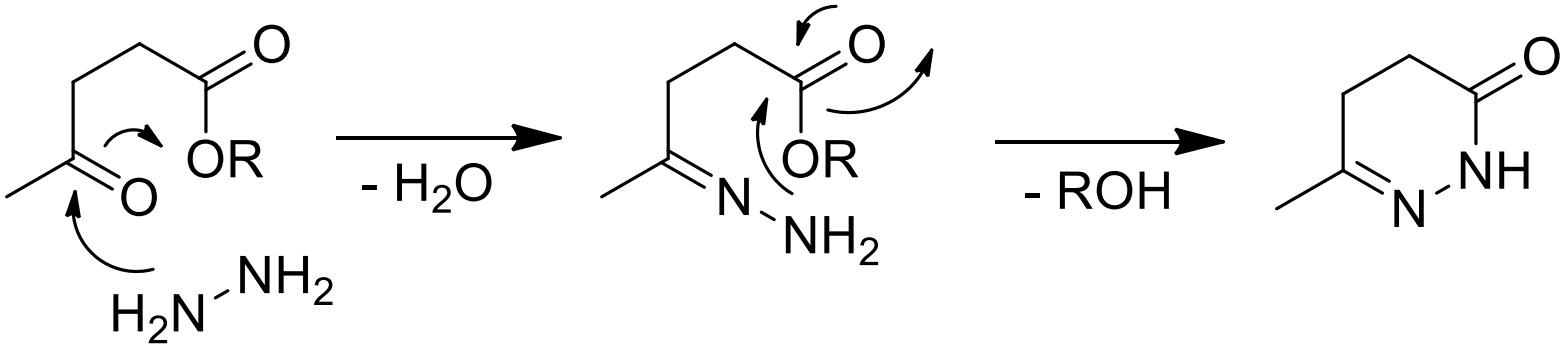
Mecanismo

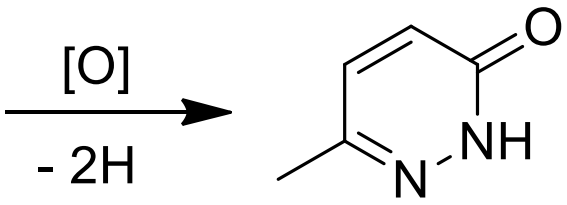


Ciclocondensação de Ácidos γ-Cetocarboxílicos ou Ésteres

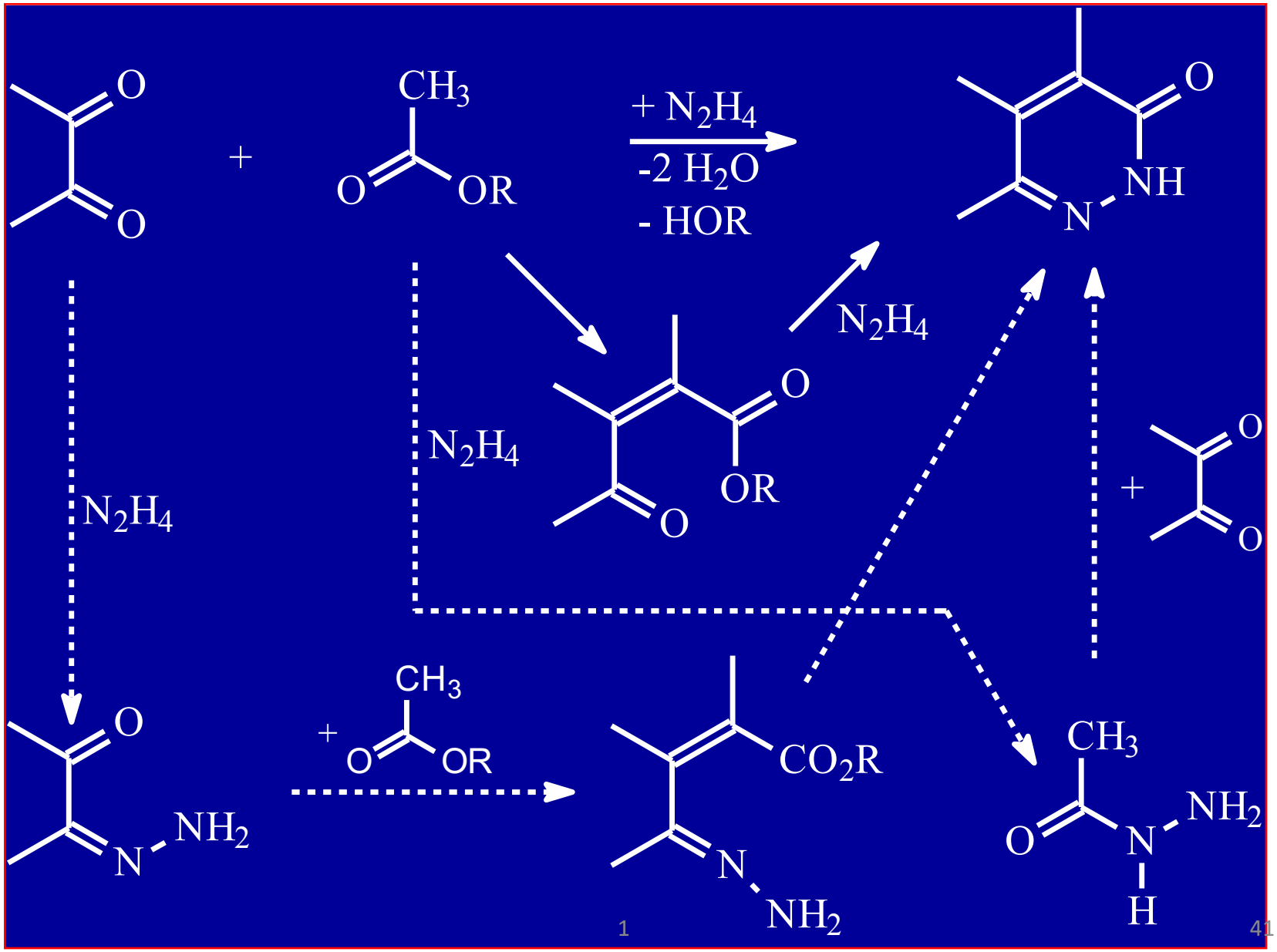


Mecanismo

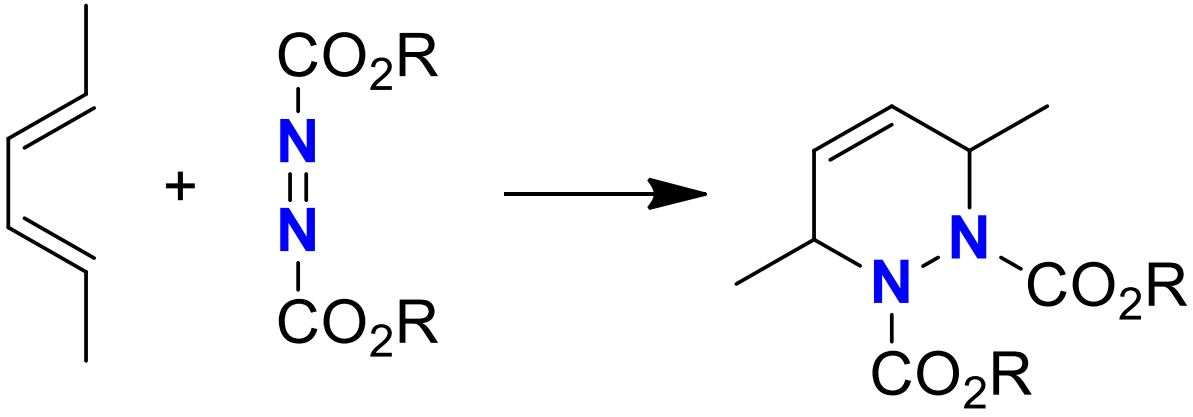




Ciclocondensação de 1,2-Dicetonas + Hidrazina



Cicloadição [4+2] – Hetero Diels-Alder



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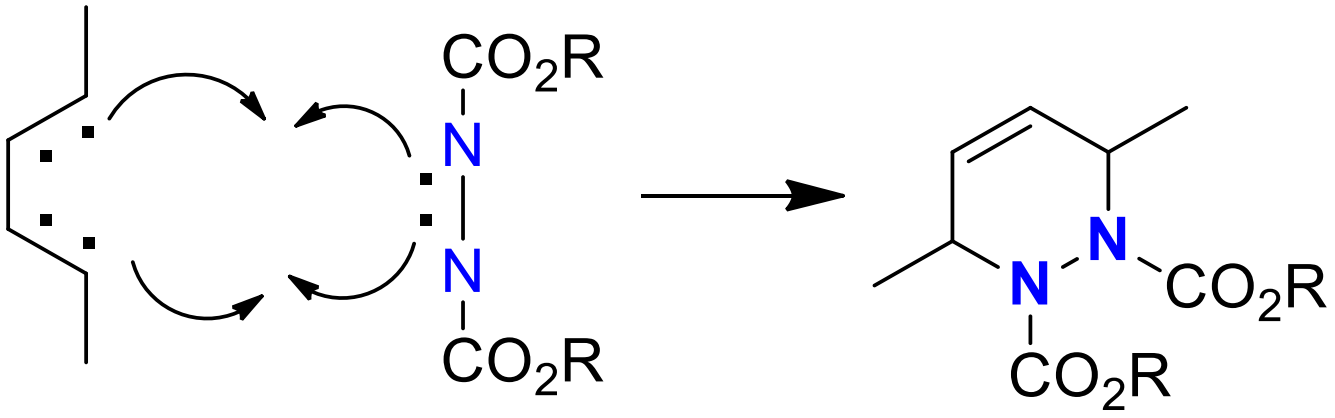
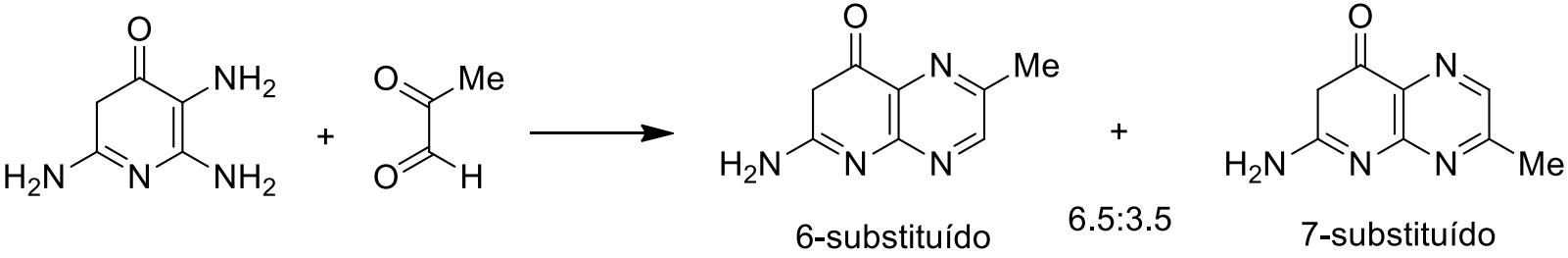


Síntese de Pteridinas

Síntese de Isay



Desvantagem: mistura de isômeros 6- e 7-substituídos

Síntese de Taylor