...doing science for better health!

Efeitos de substituintes na reatividade de sistemas aromáticos

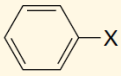
Reações de compostos aromáticos e seus mecanismos

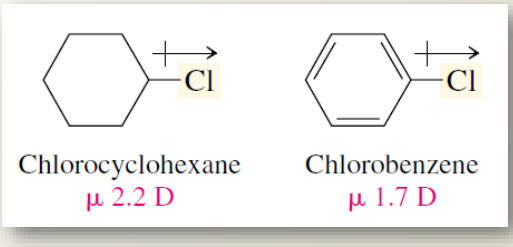
Haletos de arila: substituição nucleofílica aromática

Fenóis

...doing science for better health!

Haletos de arila

Compound	Hybridization of carbon to which X is attached	Bond energy, kJ/mol (kcal/mol)	
		X = H	X = Cl
CH_3CH_2X	sp^3	410 (98)	339 (81)
$CH_2{=}CHX$	sp^2	452 (108)	368 (88)
	sp^2	469 (112)	406 (97)

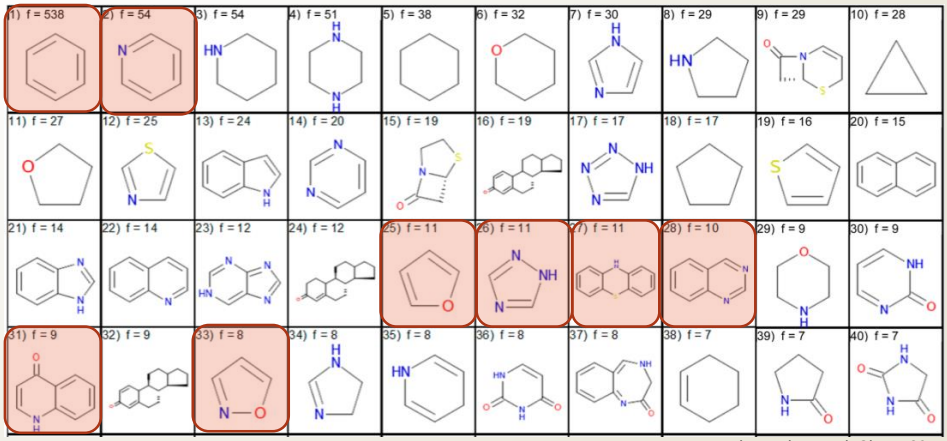


Chlorocyclohexane
μ 2.2 D

Chlorobenzene
μ 1.7 D

...doing science for better health!

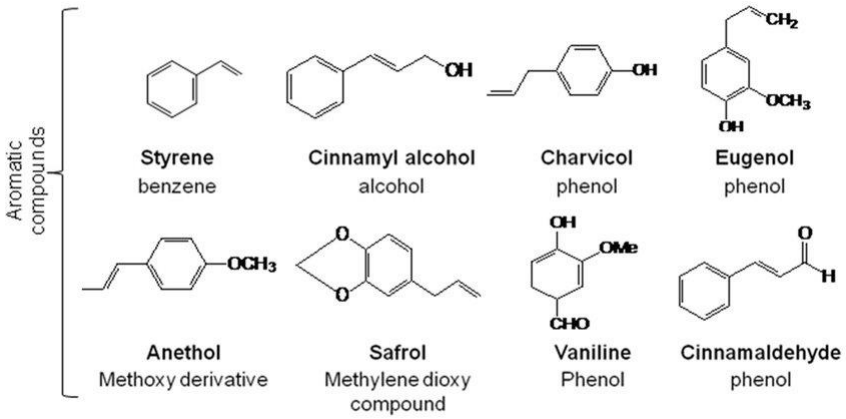
Os principais sistemas de anel usados com mais frequência em fármacos (pequenas moléculas) – FDA Orange Book



Taylor et al. J. Med. Chem. 2014

...doing science for better health!

Exemplos de compostos aromáticos encontrados em óleos essenciais de plantas



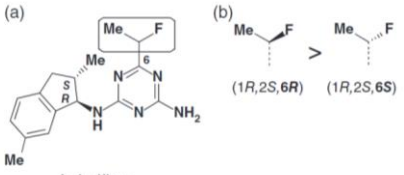
...doing science for better health!

Os halogênios são usados nas indústrias química, de água e saneamento, de plásticos, farmacêutica, de papel e celulose, têxtil, militar e de petróleo.

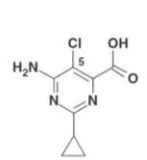
...doing science for better health!

Herbicidas

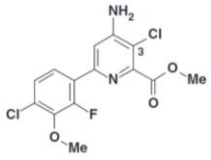
(controle de plantas daninhas)



Indaziflam



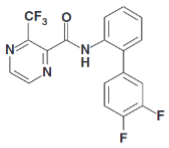
Aminocyclopyrachlor



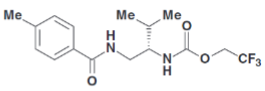
Halauxifen-methyl

Fungicidas

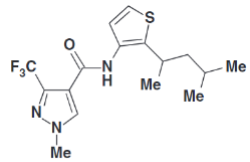
(pesticidas que destroem ou inibem a ação dos fungos que e.g. atacam as plantas



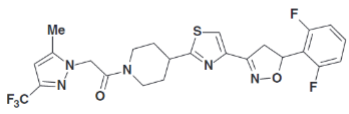
Pyraziflumid



Tolprocarb



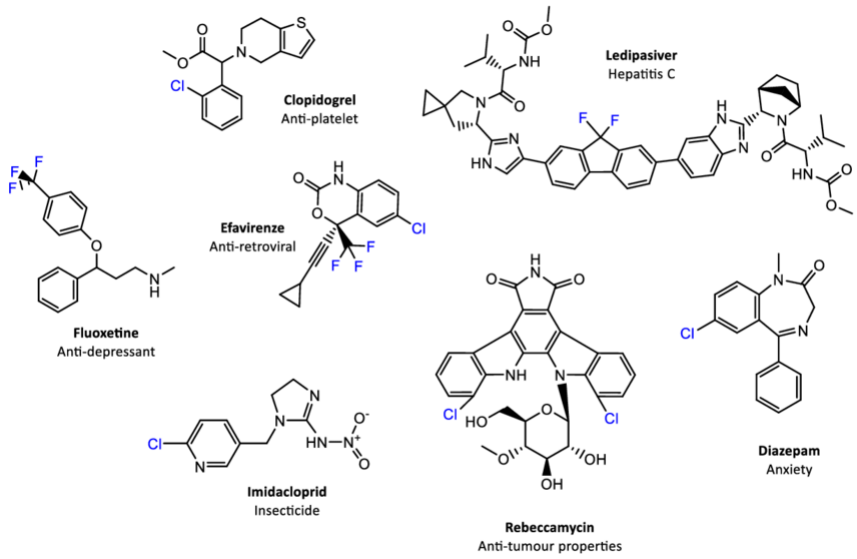
Penthiopyrad



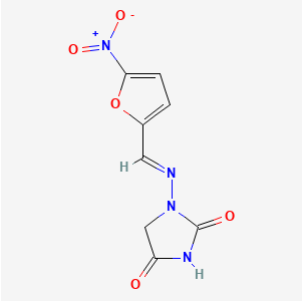
Oxathiapiprolin

...doing science for better health!

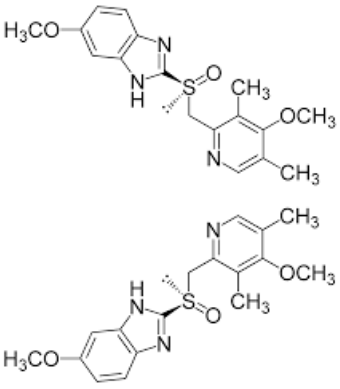
Fármacos contendo halogênios



...doing science for better health!



Nitrofurantoína
Utilizada para o tratamento de cistite e uretrite bacteriana



Omeprazol
Usado para tratar úlceras gástricas (estômago) e duodenais (intestino) e refluxo gastresofágico

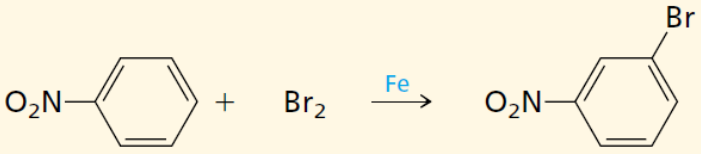
...doing science for better health!

Halogenação de arenos

General equation and specific example

$$ArH + X_2 \xrightarrow[\text{or } FeX_3]{Fe} ArX + HX$$

Arene + Halogen → Aryl halide + Hydrogen halide



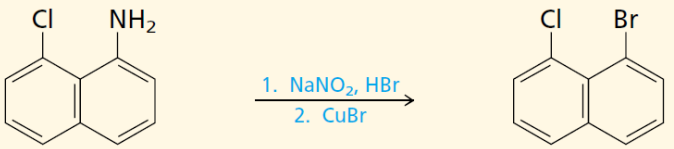
Nitrobenzene + Bromine → *m*-Bromonitrobenzene (85%)

...doing science for better health!

A reação de Sandmeyer

$$ArNH_2 \xrightarrow[2.\ CuX]{1.\ NaNO_2,\ H_3O^+} ArX$$

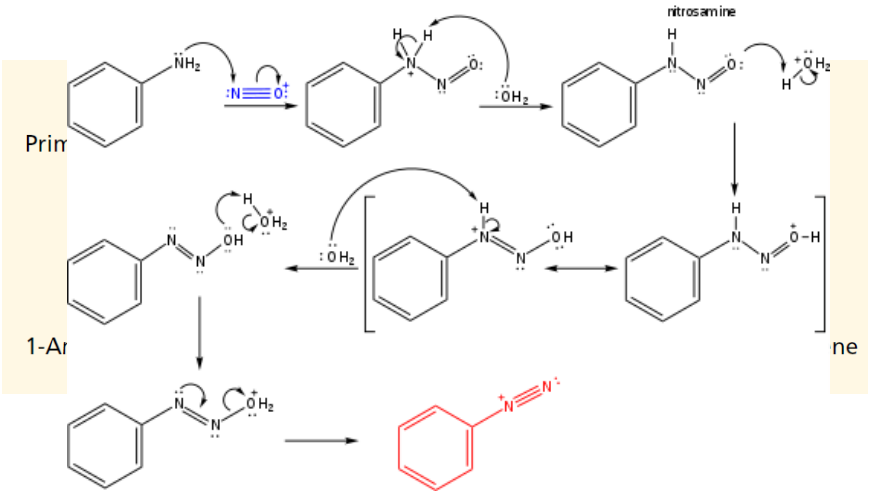
Primary arylamine → Aryl halide



1-Amino-8-chloronaphthalene → 1-Bromo-8-chloronaphthalene (62%)

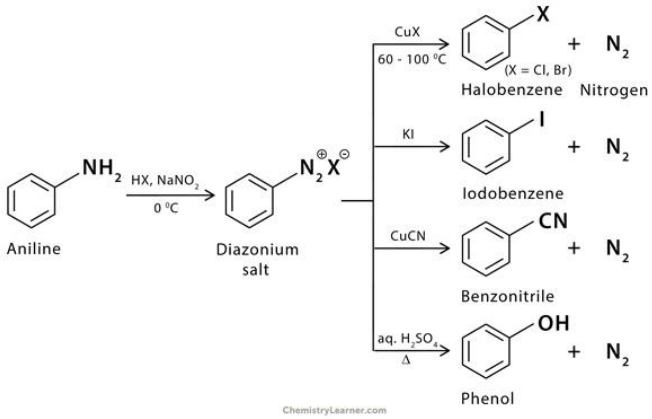
...doing science for better health!

A reação de Sandmeyer



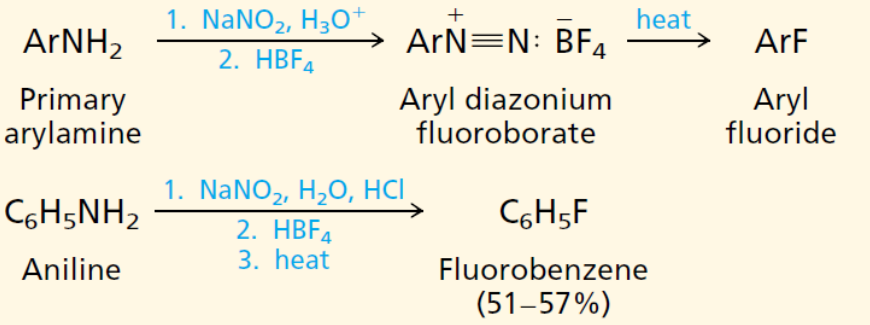
...doing science for better health!

Examples of Sandmeyer Reaction



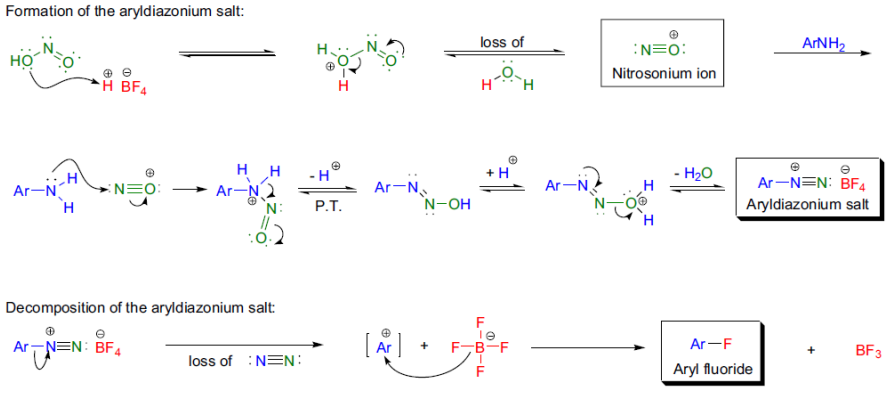
...doing science for better health!

Reação de Schiemann



...doing science for better health!

Reação de Schiemann



...doing science for better health!

Reação de sal de diazônio com o íon iodeto

$$ArNH_2 \xrightarrow[2.\ KI]{1.\ NaNO_2,\ H_3O^+} ArI$$

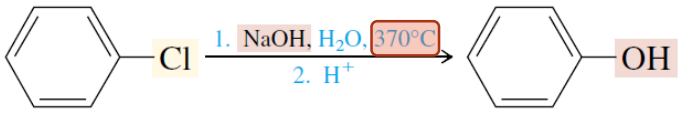
Primary arylamine — Aryl iodide

$$C_6H_5NH_2 \xrightarrow[2.\ KI]{1.\ NaNO_2,\ HCl,\ H_2O} C_6H_5I$$

Aniline — Iodobenzene (74–76%)

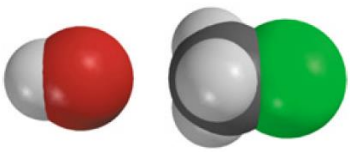
...doing science for better health!

Haletos de arila: muito menos reativos em reações de S_N

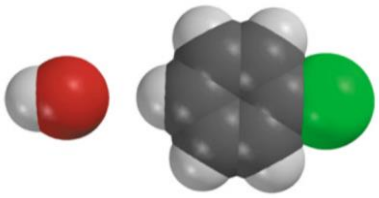


Chlorobenzene — Phenol (97%)

(*a*) Hydroxide ion + chloromethane



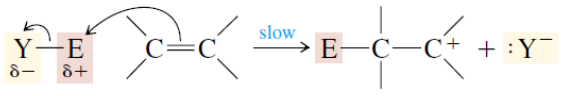
(*b*) Hydroxide ion + chlorobenzene



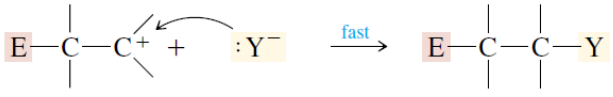
...doing science for better health!

Reações de Substituição Eletrofílica Aromática S_EAr

Lembrando...



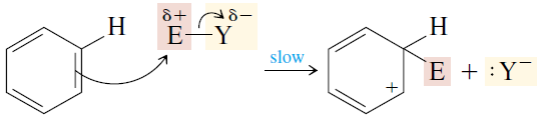
Alkene and electrophile — Carbocation



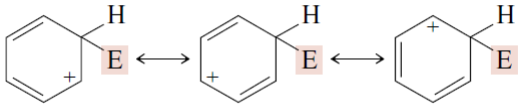
Carbocation — Nucleophile — Product of electrophilic addition

...doing science for better health!

Reações de Substituição Eletrofílica Aromática S_EAr



Benzene and electrophile — Carbocation

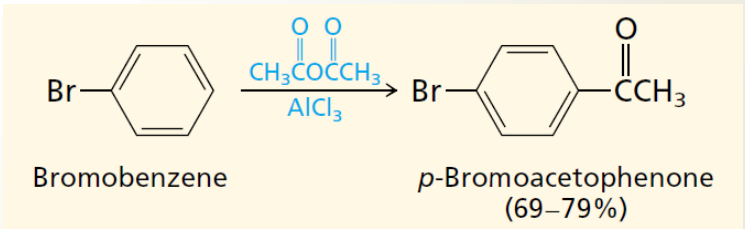


Resonance forms of a cyclohexadienyl cation

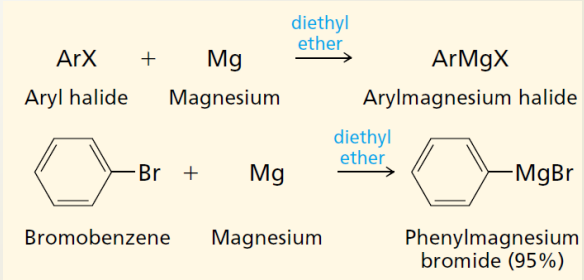
...doing science for better health!

Reações previamente estudadas

$S_{EI}Ar$

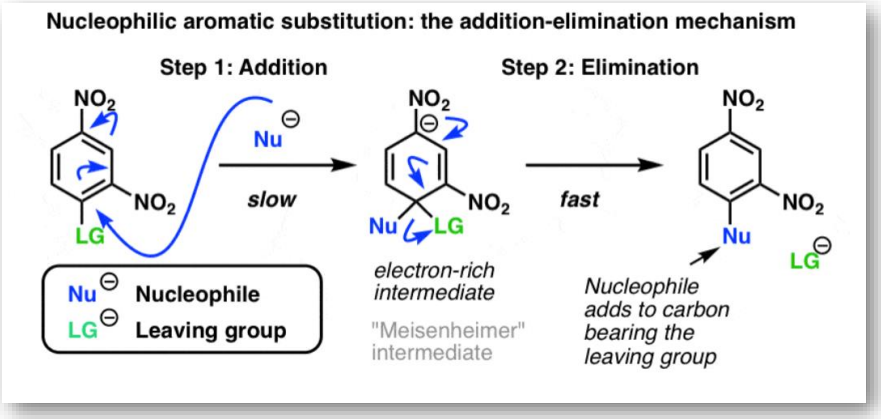


Reagentes de Grignard aromáticos



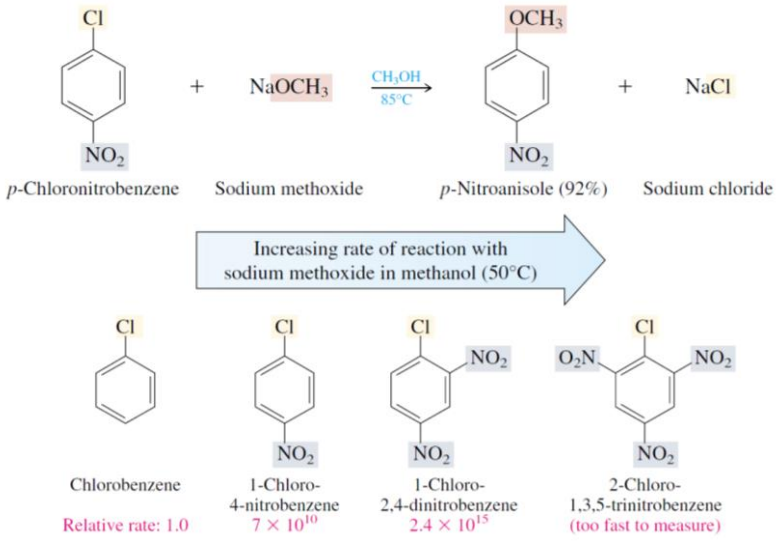
...doing science for better health!

Substituição Nucleofílica Aromática, S_NAr



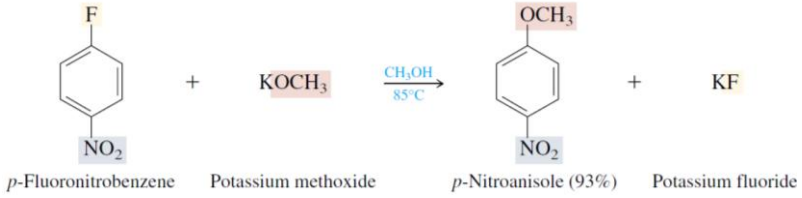
...doing science for better health!

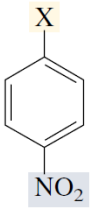
S_NAr em haletos de arila nitro-substituídos



...doing science for better health!

Reatividade de haletos de arila em reações de S_NAr





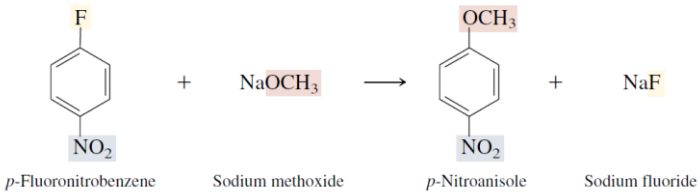
Relative reactivity toward sodium methoxide in methanol (50°C):

X = F	312
X = Cl	1.0
X = Br	0.8
X = I	0.4

$$V = k[Haleto\ de\ arila][Nu]$$

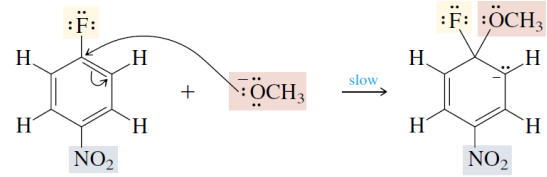
...doing science for better health!

Mecanismo de adição-eliminação na S_NAr



p-Fluoronitrobenzene | Sodium methoxide | *p*-Nitroanisole | Sodium fluoride

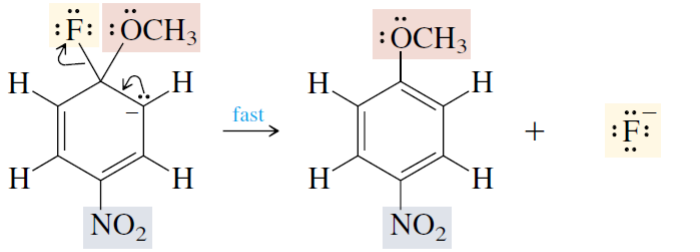
Passo 1: Adição



p-Fluoronitrobenzene | Methoxide ion | Cyclohexadienyl anion intermediate

...doing science for better health!

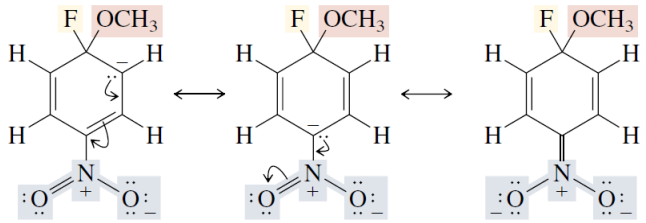
Passo 2: Eliminação



Cyclohexadienyl anion intermediate | *p*-Nitroanisole | Fluoride ion

...doing science for better health!

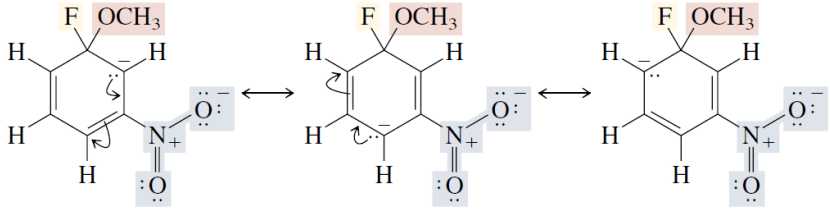
Qual é a estrutura de ressonância mais estável?



Most stable resonance structure; negative charge is on oxygen

...doing science for better health!

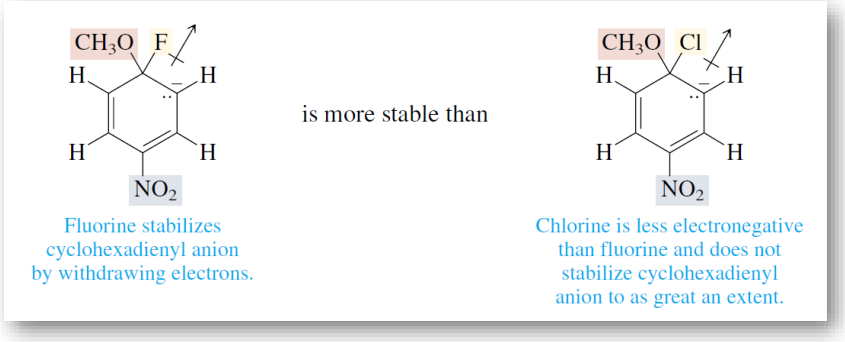
A reação de *m*-fluoronitrobenzeno com o íon metóxido é 10^5 vezes mais lenta que aquela observada para os *o*,*p*-isômeros! Por quê?



(Negative charge is restricted to carbon in all resonance forms)

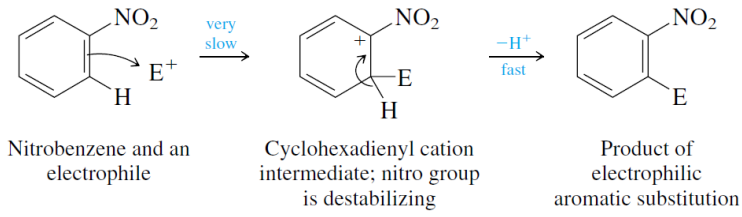
...doing science for better health!

Efeito do grupo abandonador



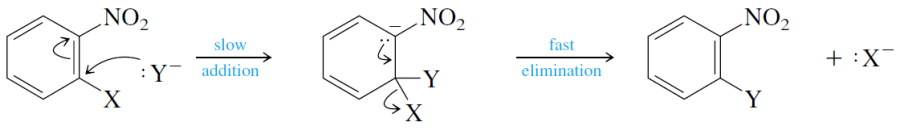
...doing science for better health!

O grupo nitro é um substituinte fortemente ***desativante*** nas reações de $S_{EI}Ar$



...doing science for better health!

O grupo nitro é um substituinte fortemente ***ativante*** nas reações de S_NAr



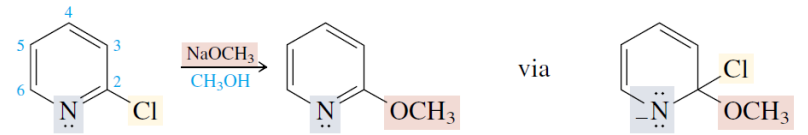
o-Halonitrobenzene (X = F, Cl, Br, or I) and a nucleophile

Cyclohexadienyl anion intermediate; nitro group is stabilizing

Product of nucleophilic aromatic substitution

...doing science for better health!

A 2-cloropiridina reage 230 mi vezes mais rapidamente com metóxido de sódio (a 50 °C) que o benzeno



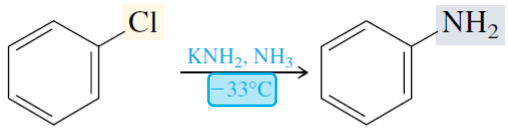
2-Chloropyridine

2-Methoxypyridine

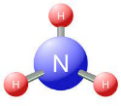
Anionic intermediate

...doing science for better health!

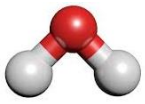
Mecanismo de adição-eliminação na S_NAr : o benzino



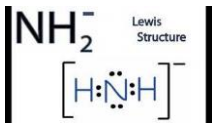
Chlorobenzene Aniline (52%)



pKa = 36



pKa = 16

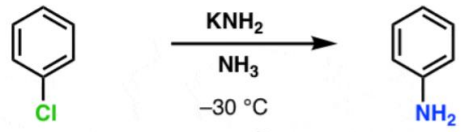


10^{20} mais básico que HO^-!

...doing science for better health!

Nucleophilic Aromatic Substitution At An Unusually Low Temperature

(1945)



chloro is only moderately electron-withdrawing

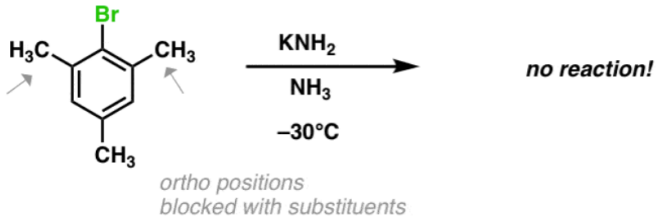
traditional S_NAr reactions require heat !

Does this also go through the addition-elimination mechanism?

...doing science for better health!

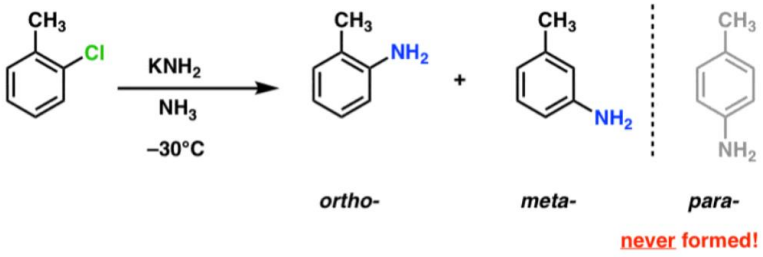
Um mecanismo de adição-eliminação não parece apropriado!

Observation #1: no reaction occurs without *ortho*- hydrogens!



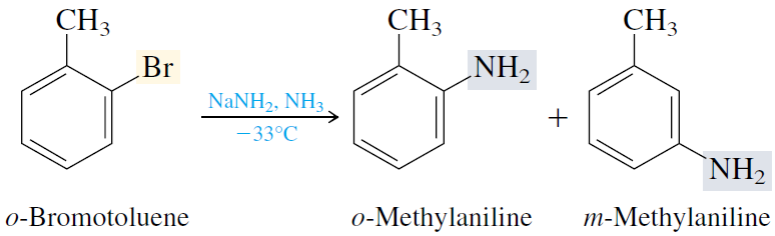
...doing science for better health!

Observation #2 : in this example, the *ortho*- and *meta*- products are formed, but none of the *para*- is observed

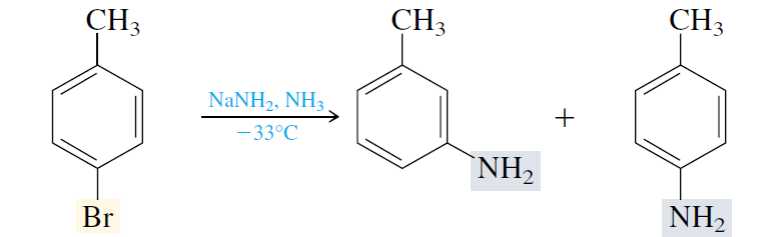


...doing science for better healt

Regioquímica da reação



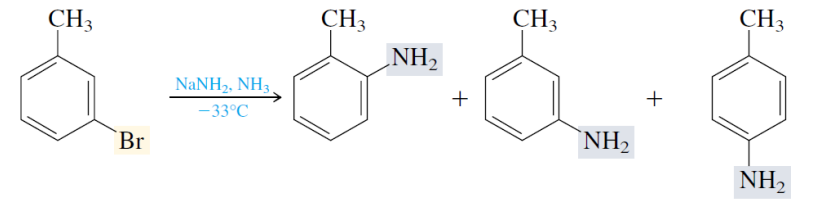
o-Bromotoluene | *o*-Methylaniline | *m*-Methylaniline



p-Bromotoluene | *m*-Methylaniline | *p*-Methylaniline

...doing science for better health!

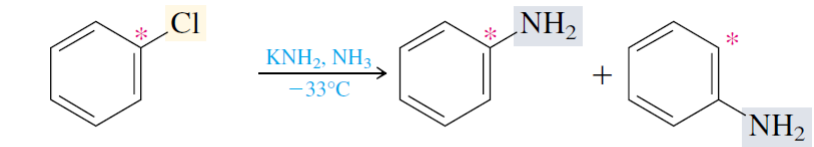
As *o*-, *m*- e *p*-metilanilinas são formados a partir do *m*-bromotolueno!



m-Bromotoluene | *o*-Methylaniline | *m*-Methylaniline | *p*-Methylaniline

...doing science for better health!

Mecanismo de John D. Roberts em 1953



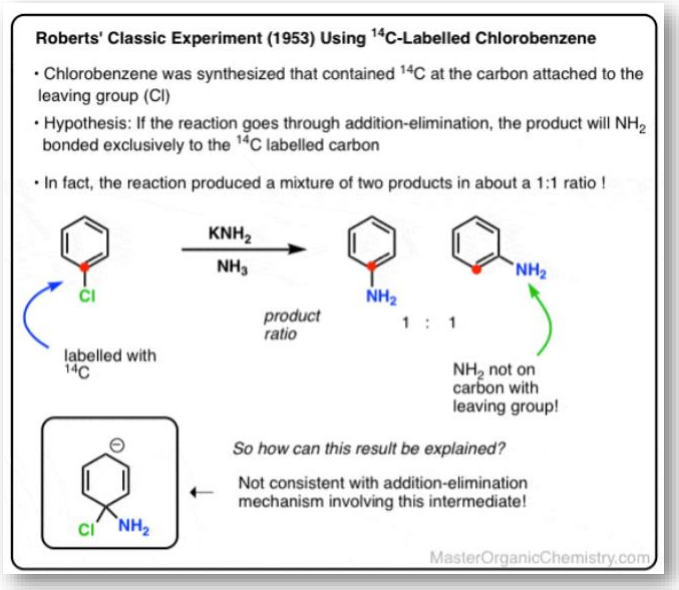
Chlorobenzene-1-^{14}C (* = ^{14}C)

Aniline-1-^{14}C (48%)

Aniline-2-^{14}C (52%)

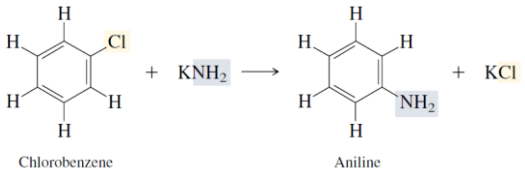
...doing science for better health!

Isso não é consistente com um mecanismo de adição-eliminação!



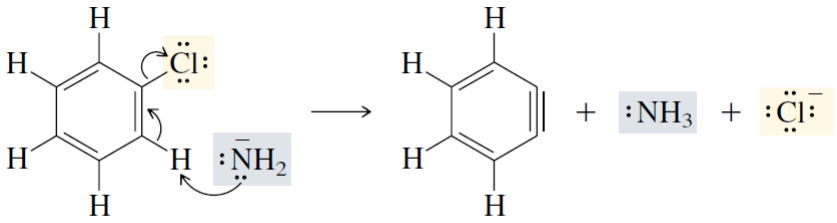
...doing science for better health!

Mecanismo de adição-eliminação na S_NAr : o benzino



Chlorobenzene Aniline

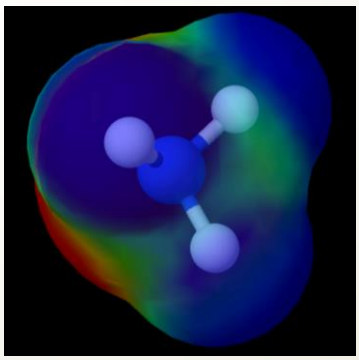
Passo 1: Eliminação

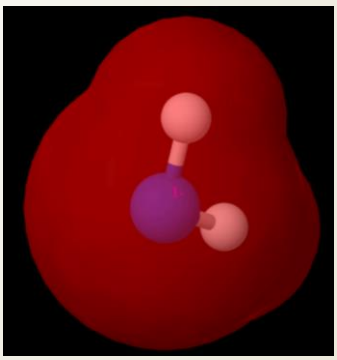


Chlorobenzene Benzyne

...doing science for better health!

Mapas de potencial eletrostático: Amônia e amideto





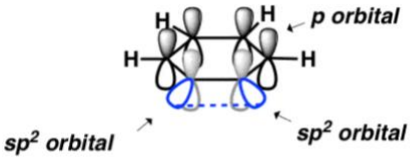
...doing science for better health!

"Benzyne"

O benzino

Not a "typical" triple bond

The triple bond is formed from the overlap of two sp^2 orbitals

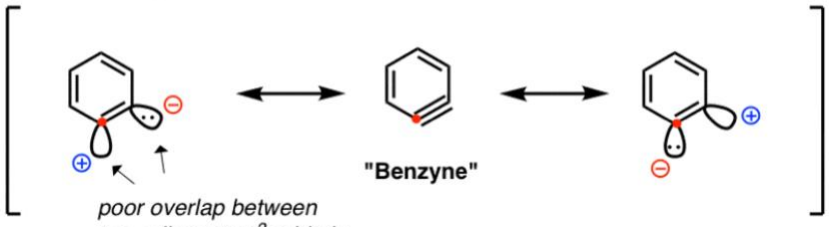


Note that sp^2 orbitals involved in the "triple bond" are at 90° to the p orbitals of the aromatic pi system → poor overlap leads to a very weak triple bond, easily broken by a nucleophile

(estimated strain energy = 50 kcal/mol)

...doing science for better health!

Sometimes helpful to think of the triple-bonded form as being in resonance with two "charged" forms:

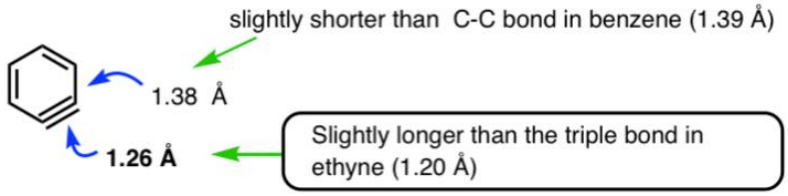


poor overlap between two adjacent sp^2 orbitals

...doing science for better health!

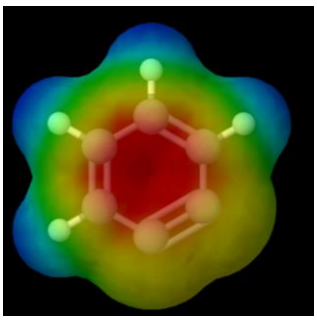
Benzeno & Benzino

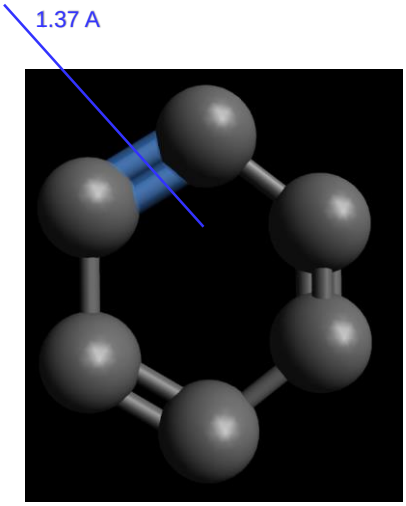
Bond lengths in benzyne

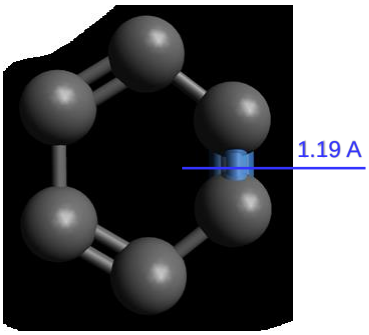


...doing science for better health!

Benzeno & Benzino



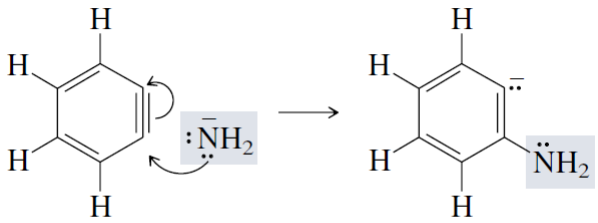




...doing science for better health!

Mecanismo de adição-eliminação na S_NAr : o benzino...

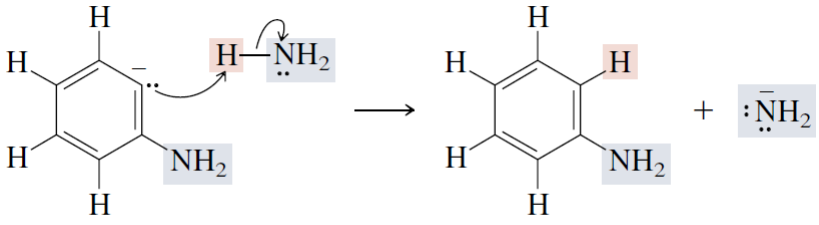
Passo 2: Início da fase de adição



Benzyne Aryl anion

...doing science for better health!

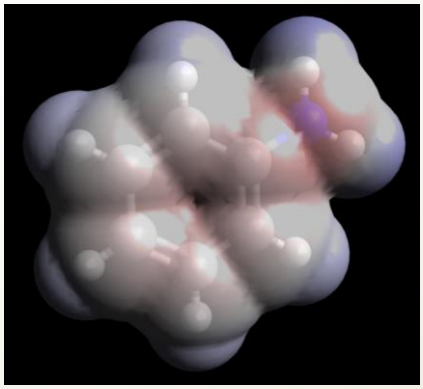
Mecanismo de adição-eliminação na S_NAr : o benzino...

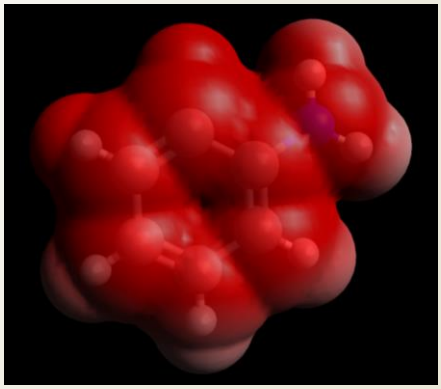


Aryl anion Aniline

...doing science for better health!

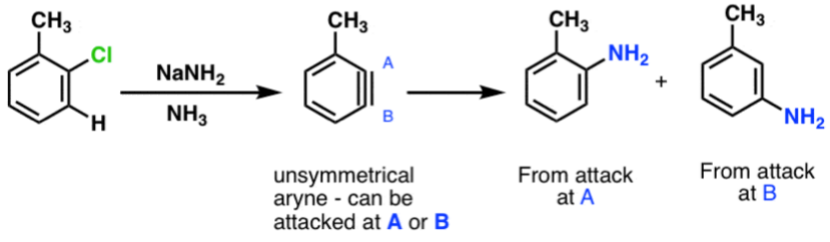
Anilina & Ânion arila





...doing science for better health!

Substituted benzynes ("arynes") can produce multiple products



unsymmetrical aryne - can be attacked at **A** or **B**

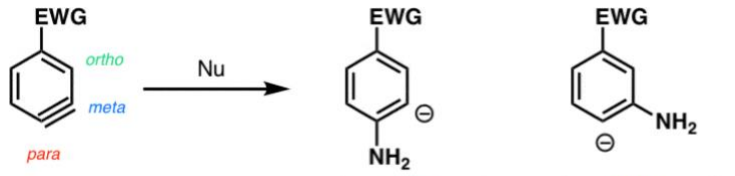
From attack at A

From attack at B

...doing science for better health!

When an electron-withdrawing group (EWG) is present, the intermediate where the negative charge is closest to the EWG will be favored

Case #1 - triple bond between meta and para carbons:



Aryne

from para attack negative charge closer to EWG

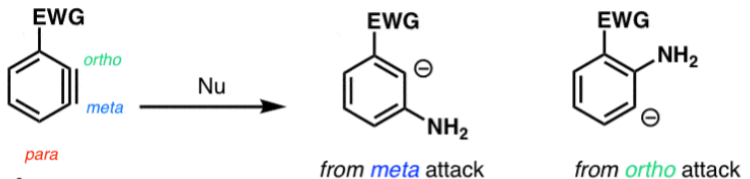
Favored

from meta attack negative charge farther from EWG

Disfavored

...doing science for better health!

Case #2 - triple bond between ortho and meta carbons:



Aryne

from meta attack negative charge closer to EWG

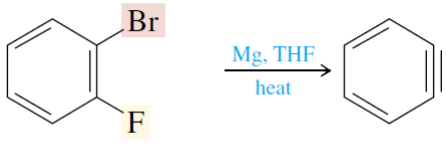
Favored

from ortho attack negative charge farther from EWG

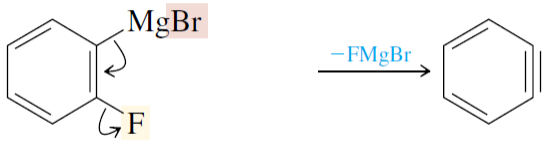
Disfavored

...doing science for better health!

A reação de Diels-Alder do benzeno

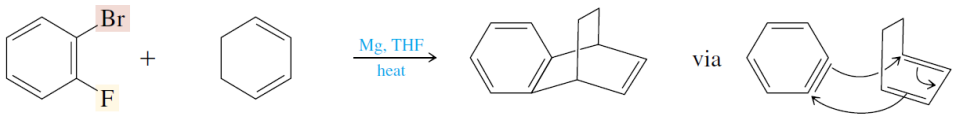


o-Bromofluorobenzene Benzyne



o-Fluorophenylmagnesium bromide Benzyne

...doing science for better health!



o-Bromo-fluorobenzene 1,3-Cyclohexadiene 5,6-Benzobicyclo[2.2.2]-octa-2,5-diene (46%)