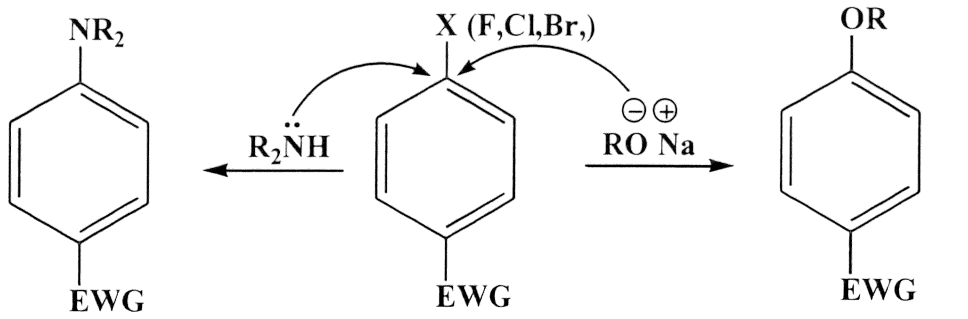
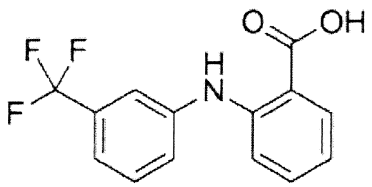
Nucleophilic aromatic substitution : formation of aromatic amines and ethers:

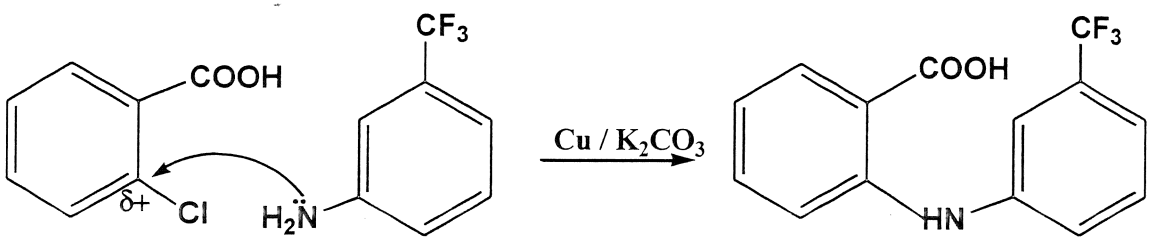


armatic amine aromatc halide arylalkyl ether

The formation of aromatic amines (synthesis Flufenamic acid (NSAIDs))



2-{[3-(Trifluoromethyl)phenyl]amino}benzoic acid



Flufenamic acid

C. Elimination reactions of alkyl halides and alcohols

Elimination reactions of alkyl halides and alcohols

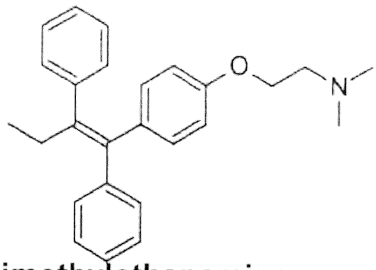
- Substitution competes with elimination
- The ease of elimination: 3° halides > 2° > 1°

$$RCH_2\text{——}CH_2Br \xrightarrow[\text{(KOH)}]{\text{strong base}} RCH{=}CH_2 + H_2O + KBr$$

$$RCH_2\text{——}CH_2OH \xrightarrow[\text{heat}]{H_2SO_4} RCH{=}CH_2 + H_2O$$

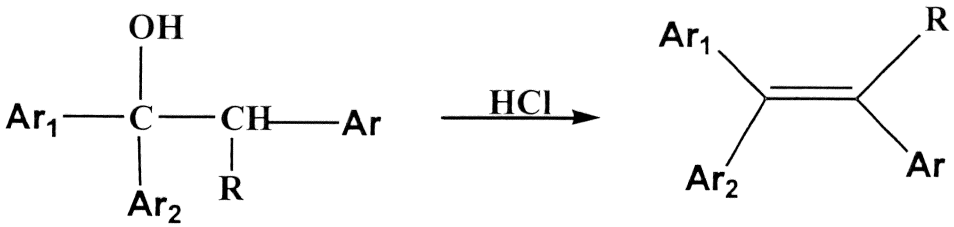
$$RCH_2\text{——}CH_2OH \xrightarrow[\text{pyridine}]{POCl_3} RCH{=}CH_2 + H_2O$$

Elimination reactions on alcohols: Synthesis of Tamoxifen



(*Z*)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-*N*,*N*-dimethylethanamine

- Tamoxifen is a competitive inhibitor of Estradiol (SERMs): It is currently used for the treatment of estrogen receptor ER)-positive (ER+) breast cancer in women
- Tamoxifen acts in bones as ER agonist



E and Z isomers

(Z) isomer ,isolated by fractional crystallization

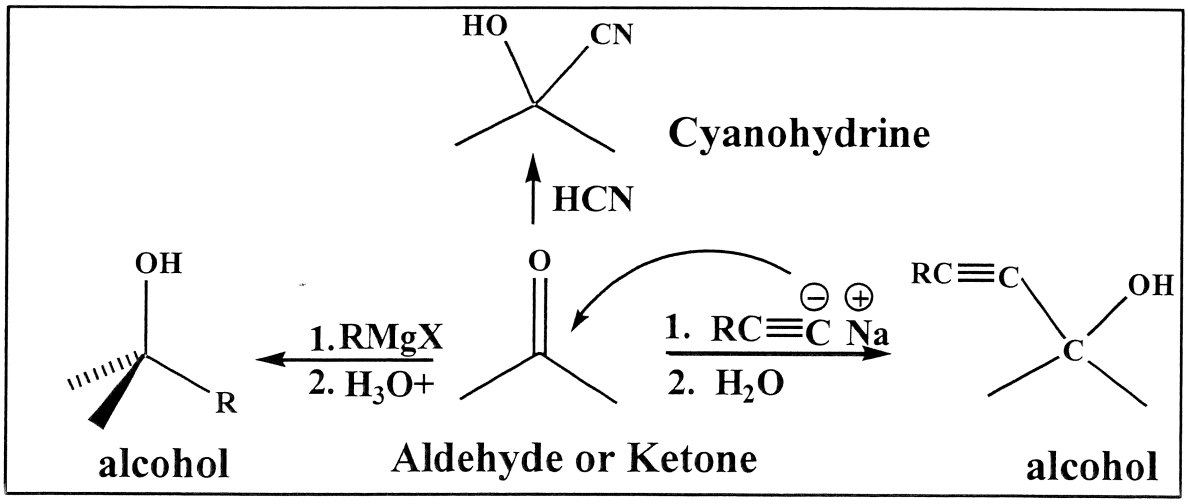
Drug Synthesis

الاصطناع (التخليق) الدوائي

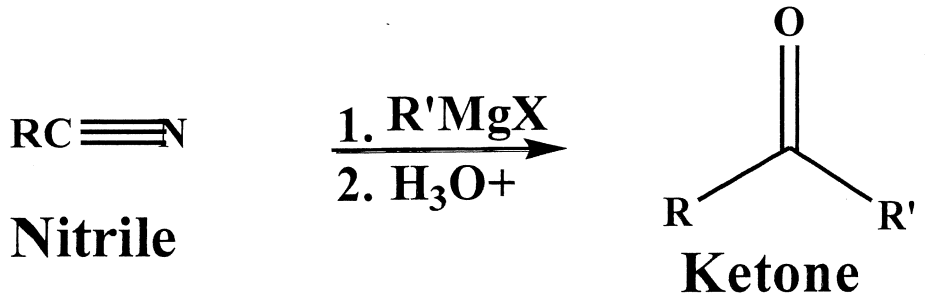
Some types of reactions used in drug synthesis

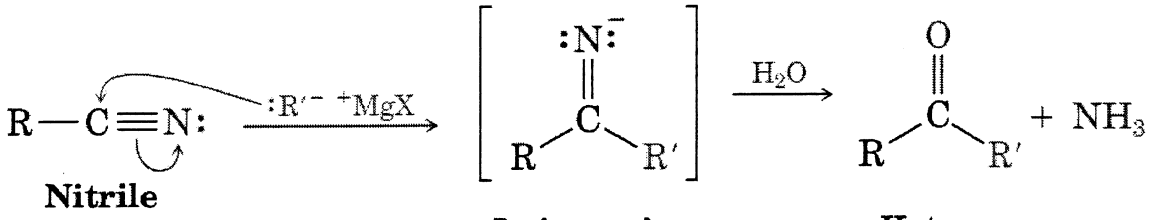
7. Nucleophilic addition to carbonyl

Nucleophilic addition to carbonyl:Formation Of Cyanohydrine, Acetylenic Alcohol, and Alcohols

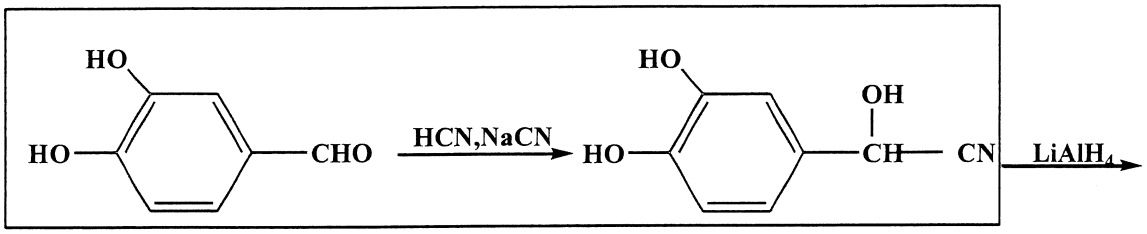


Nucleophilic addition of RMgX to Nitrile: Formation of Ketones



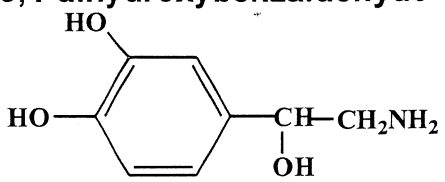


Addition of HCN to aldehydes : (synthesis of norepinephrine)

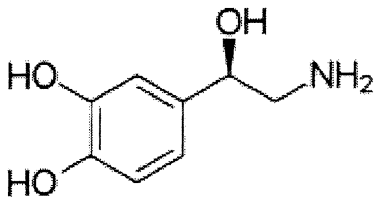


3,4-dihydroxybenzaldehyde

2-Hydroxy-2-(3,4-dihydroxyphenyl) acetonitrile

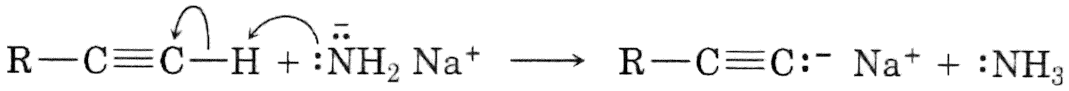


Racemic Norepinephrine

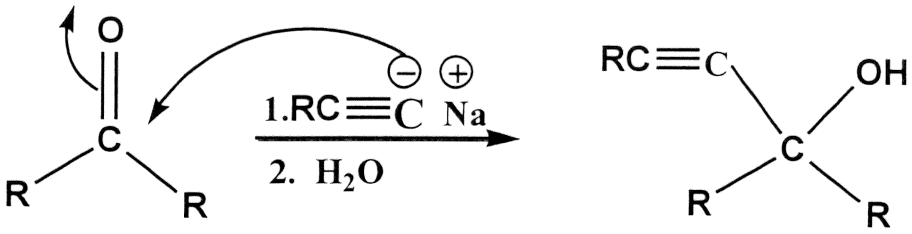


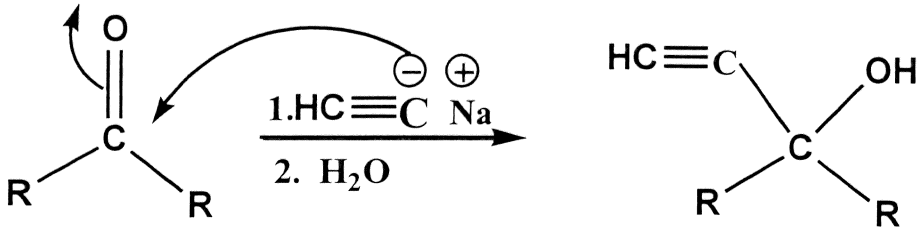
(R)-4-(2-amino-1-hydroxyethyl)benzene-1,2-diol

Addition of Acetylide anion to ketones



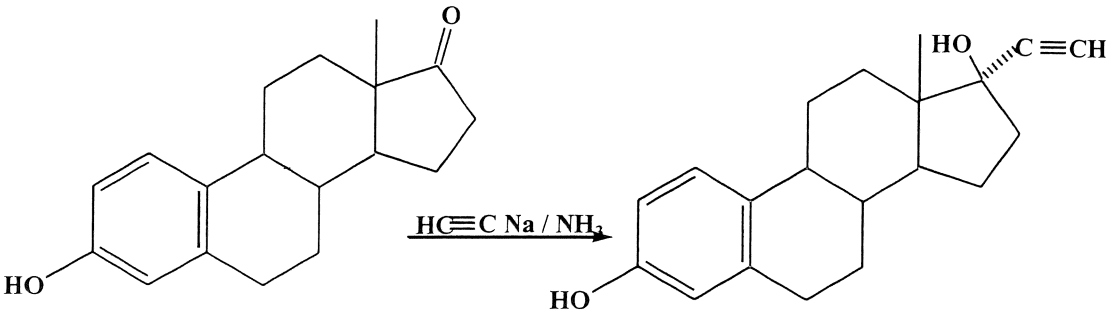
Acetylide anion





Addition of Ethynylide anion to ketones: Synthesis of Ethinyl estradiol

- Nucleophilic addition of sodium ethynylide to C17-keto group

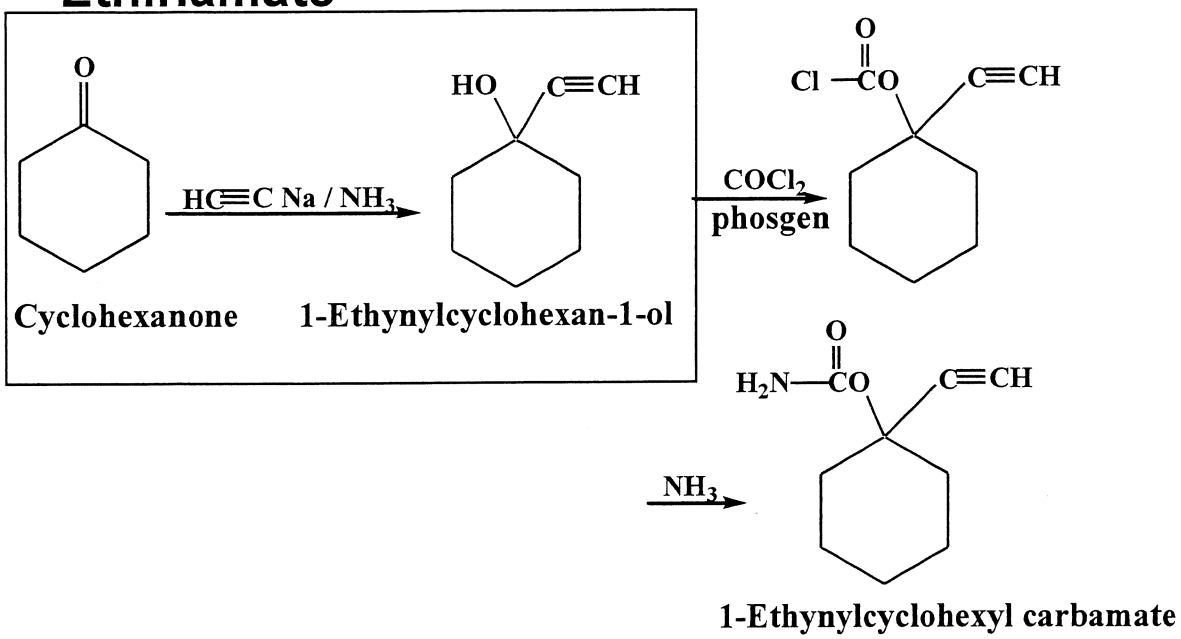


Estrone

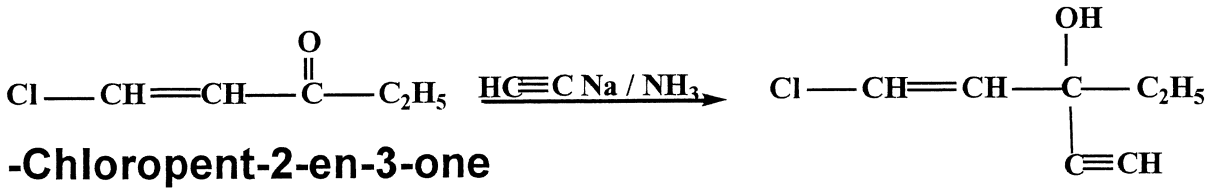
Ethinyl estradiol

19-nor-17α-pregna-1,3,5(10) trien-20-yn-3,17-diol

Addition of Ethynylide anion to ketones: Synthesis of the Sedative- hypnotic Ethinamate



Addition of Ethynylide anion to ketones: Synthesis of the Sedative-Hypnotic Ethchlorvynol



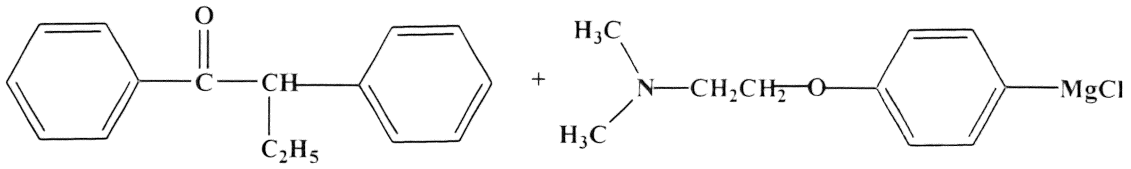
1-Chloropent-2-en-3-one

Ethchlorvynol

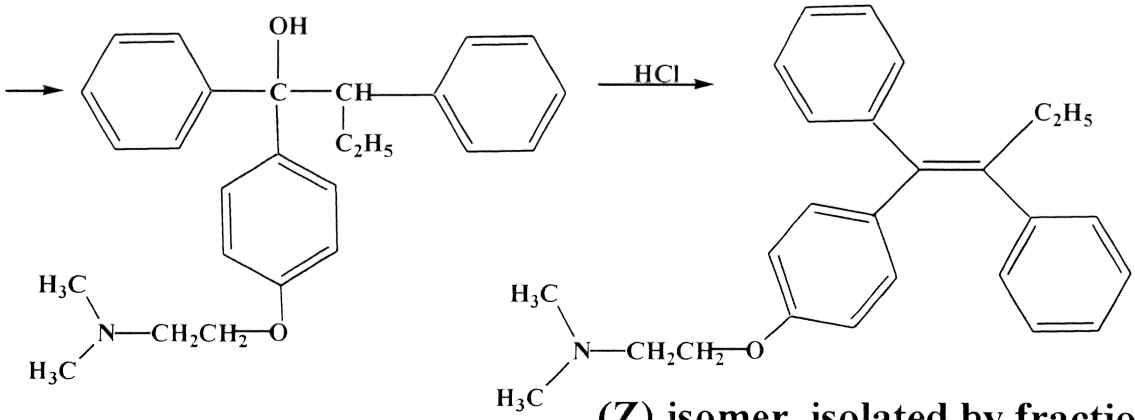
1-Chloro-3-ethylpent-1-en-4-yn-3-ol

Addition of RMgX to ketones: synthesis of Tamoxifen (TMX)

- Tamoxifen is an competitive inhibitor of Estradiol

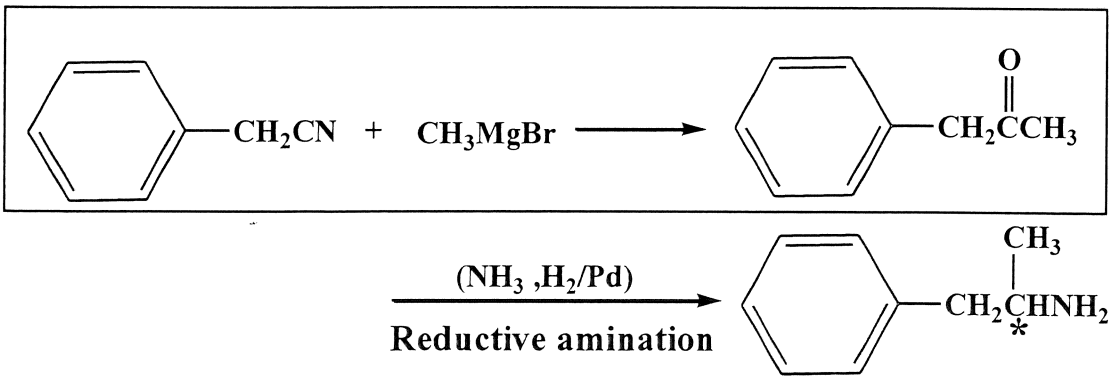


α-Ehyldesoxybenzoin



(Z) isomer ,isolated by fractional crystallization

Addition of RMgX to Nitriles:Synthesis of the CNS stimulant: Amphetamine



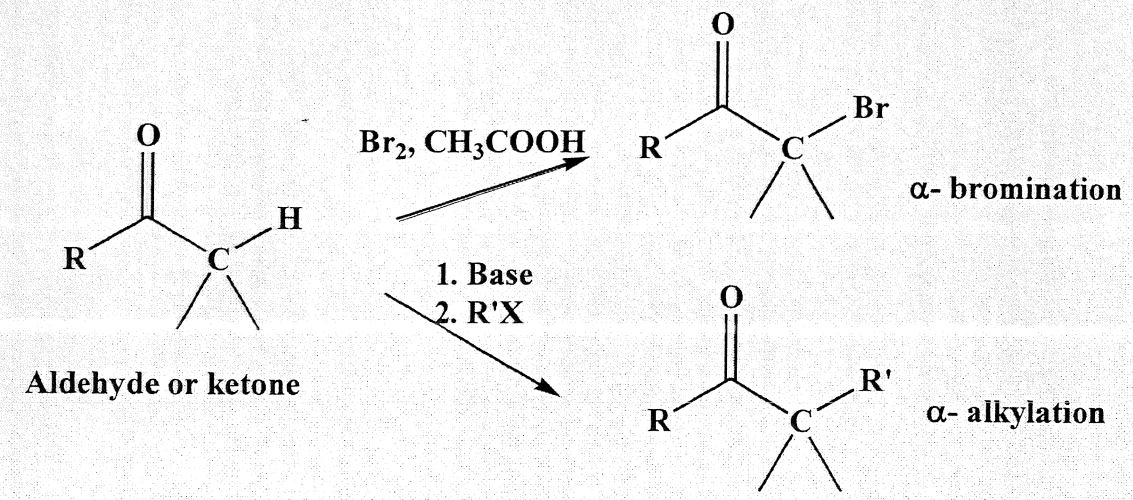
Amphetamine

Drug Synthesis
الاصطناع (التخليق) الدوائي

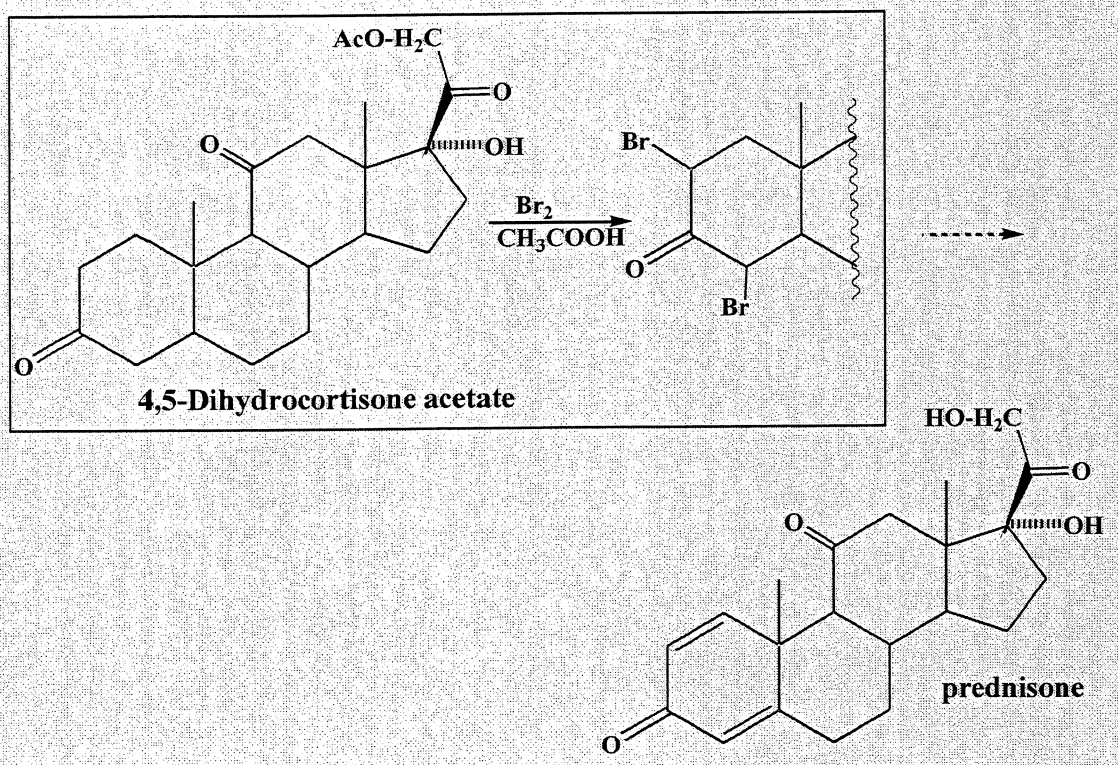
Some types of reactions used in drug synthesis
8.Carbonyl-α- substitution reactions

Carbonyl-α- halogenation and alkylation

- Bromination of aldehydes and ketones in acidic medium through enol form
- Alkylation of aldehydes,ketones, nitriles and esters: using strong base to form enolate which then alkylated by R-X



α-Bromination : Synthesis of the glucocorticoidal Prednisone (formation of Dienone system)



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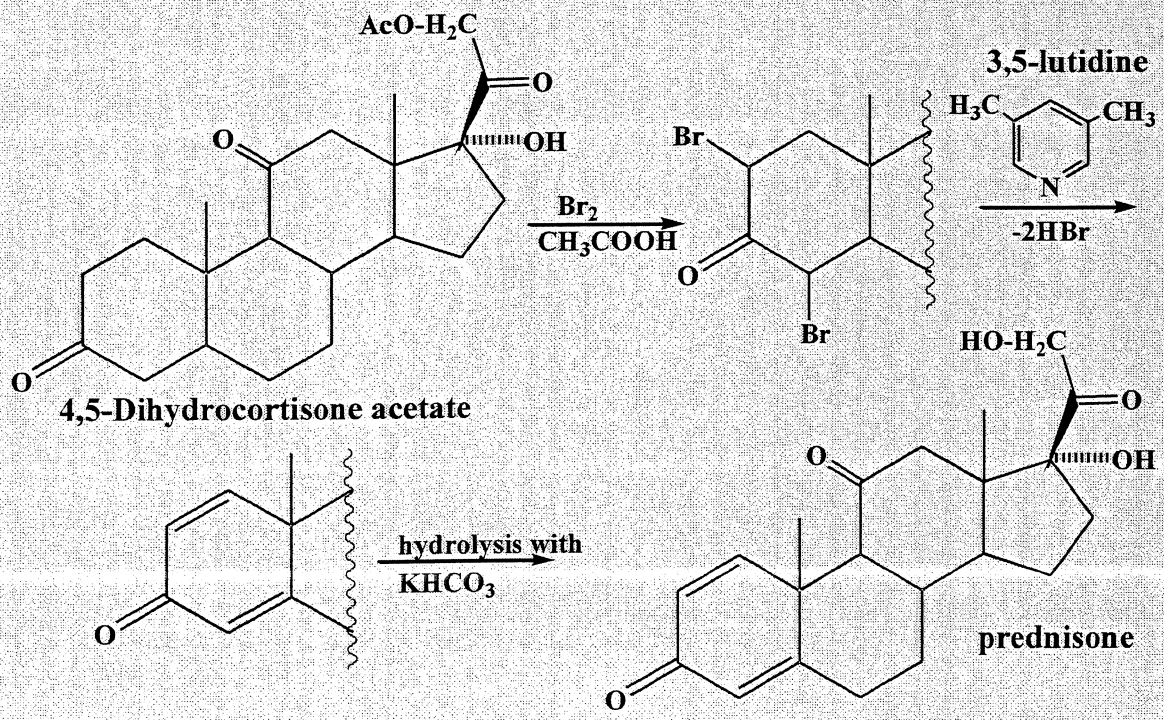

17α,21-dihydroxypregna-1,4-dien-3,11,20-trione