Hydrogenolysis

• Hydrogenolysis performs reduction with the concomitant bond rupture such as the elimination of the benzyl protecting group from amines or alcohols

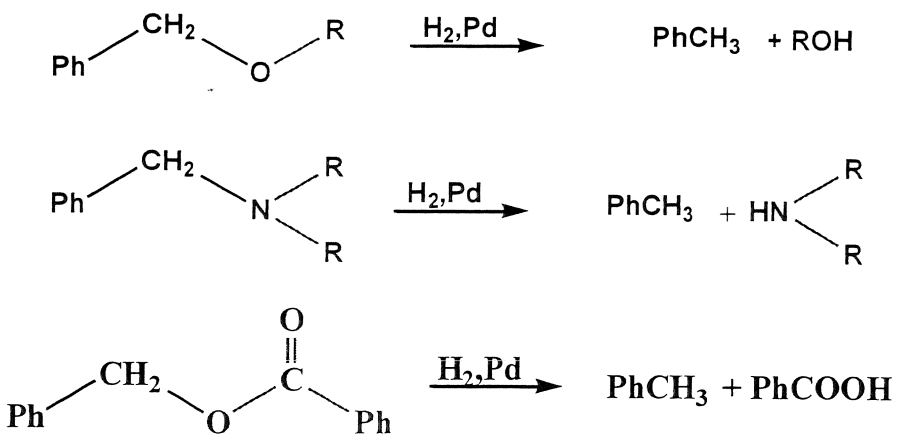
$$ArCH_2\text{——}NR_2 \xrightarrow{H_2\ /\ catalyst} ArCH_3 + HNR_2$$

$$ArCH_2\text{——}OR \xrightarrow{H_2\ /\ catalyst} ArCH_3 + ROH$$

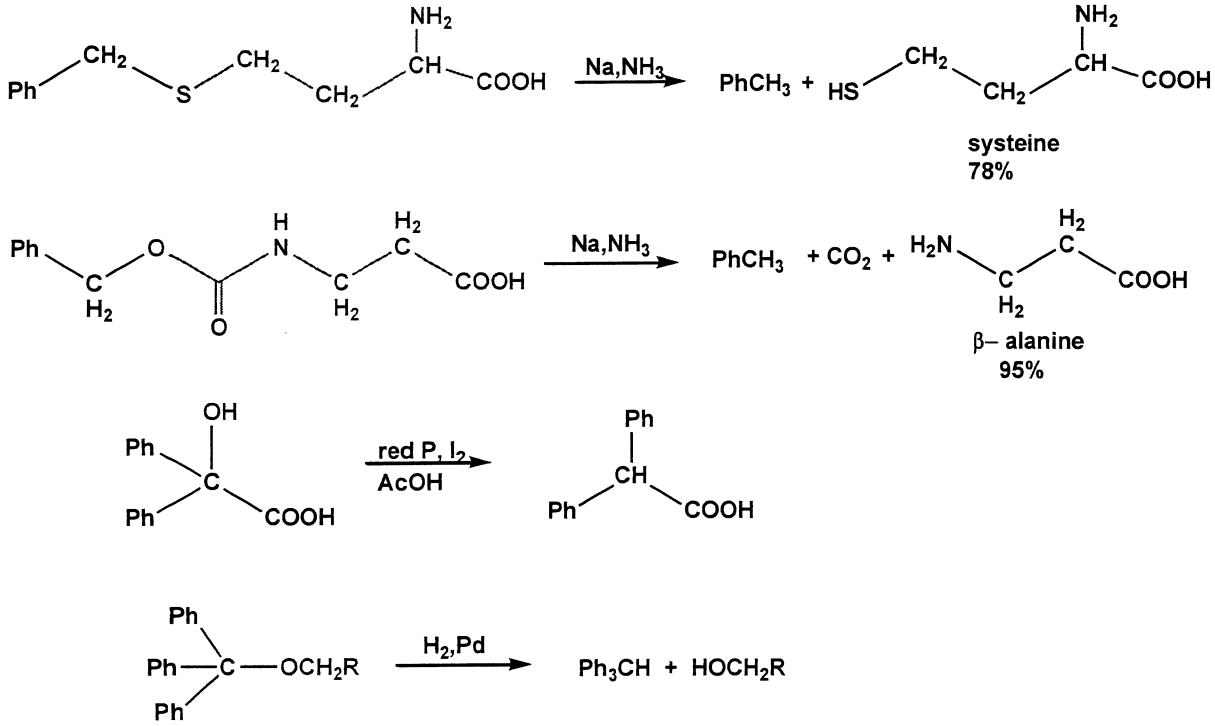
Hydrogenolysis of benzylic system

• The benzylic group when attached to OR, NR_2 , OCOR ..., is particularly susceptible to be reduced with the concomitant bond rupture.

• Catalytic reduction is widely used than the other methods

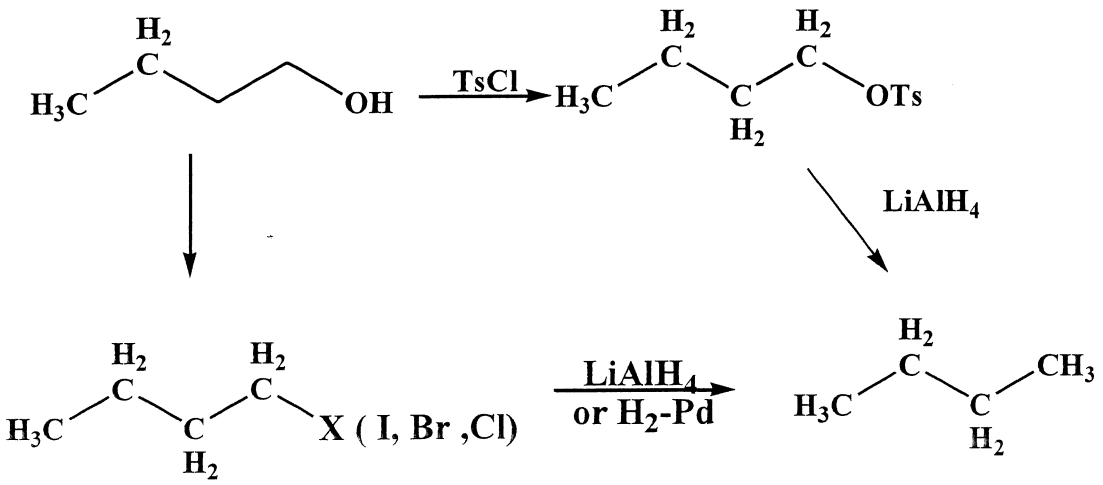


Hydrogenolysis of benzylic system



Hydrogenolysis of alcohols via Tosylaes or Halides

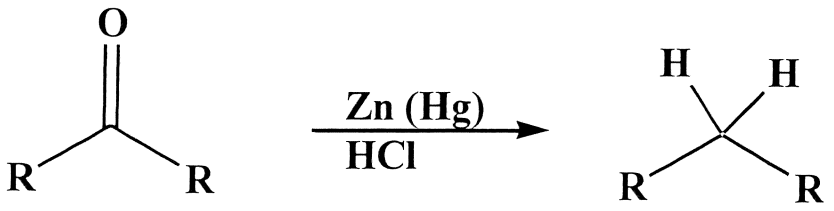
- OH function may be got rid of via toluene-p-sulfonates or via halides



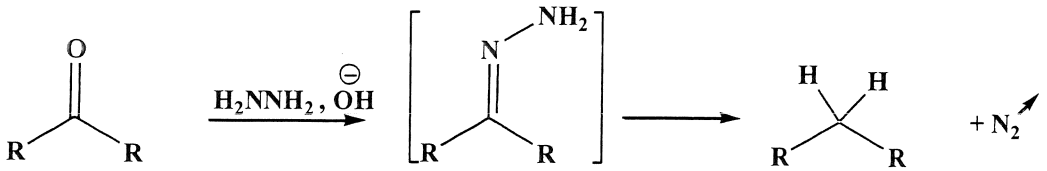
Reduction of carbonyl C=O to CH_2

Reduction of carbonyl C=O to alkanes

- **Clemmensen method**



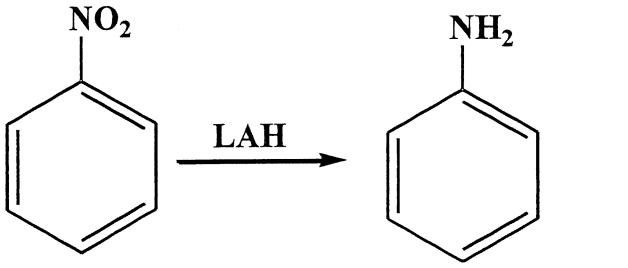
- **Wolf Kishner method**

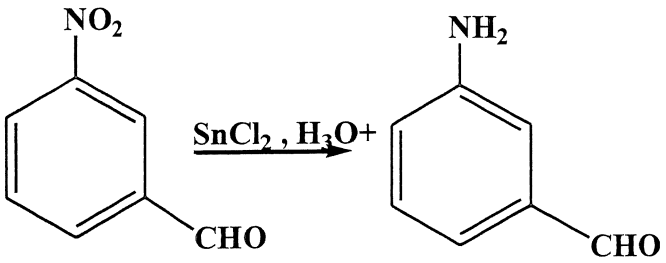


Hydrazone

Reduction of aromatic nitro-compounds

- NO_2 can be reduced to NH_2 by, $LiAlH_4$, H_2/Ni and Zn/HCl
- Selective reduction is possible by stannous chloride

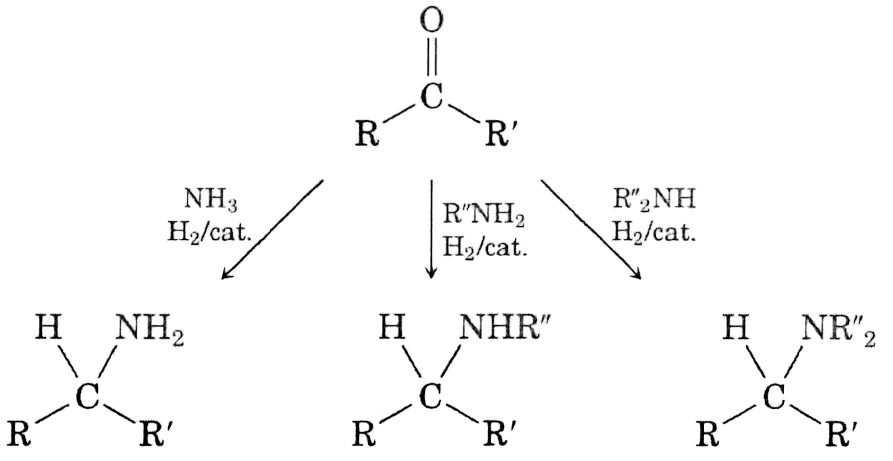




Reductive Amination of aldehydes and ketones

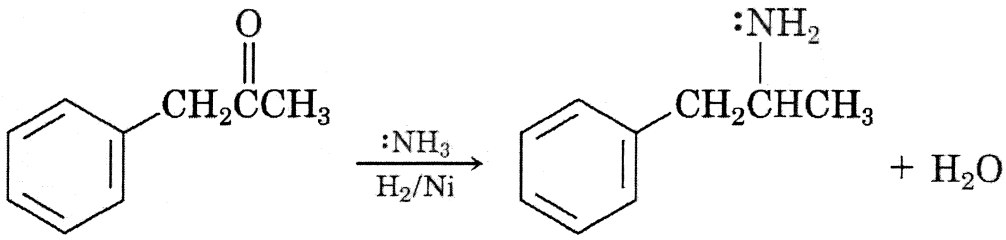
Reductive amination of ketones

- Addition of NH_3, primary or secondary amines to ketones combined with catalytic hydrogenation yield amines



Primary amine **Secondary amine** **Tertiary amine**

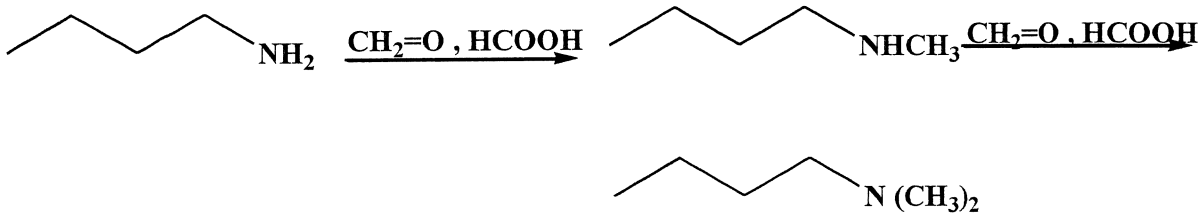
Reductive amination of ketones: Synthesis of amphetamine and methamphetamine



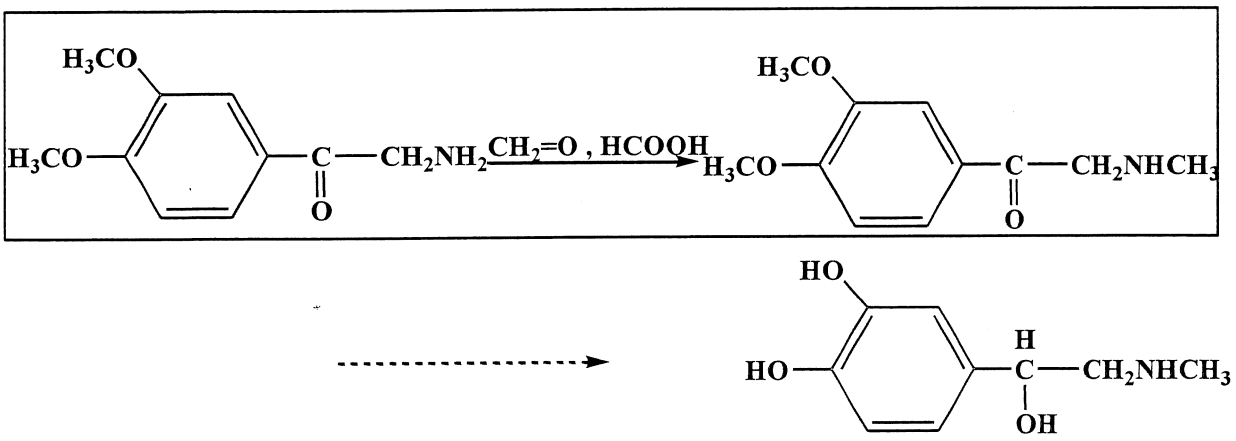
Phenyl-2-propanone **Amphetamine**

Reductive amination of formaldehyde: Methylation of amines (Eschweiller-Clark reaction)

•Addition of 1^0 or 2^0 amine to CH_2=O in the presence of HCOOH as reducing agent



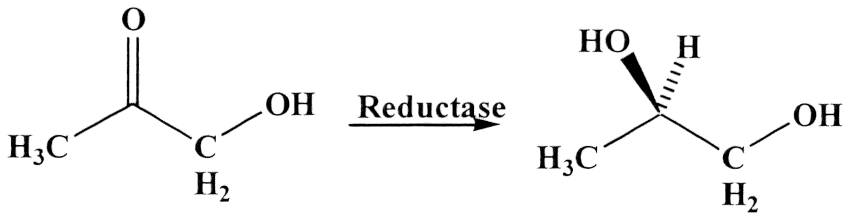
Eschweiller-Clark reaction, Synthesis of Epinephrine



Epinephrine

Enzymatic reduction (stereospecific reduction)

- Incubation of 1-hydroxypropan-2-one with yeast reductase at 32° for 3 days yields (2R)-propane-1,2-diol or (R)-propyleneglycol
- Reaction is stereospecific; gives (R)-Enantiomer



1-hydroxypropan-2-one **(2R)-Propane-1,2-diol**

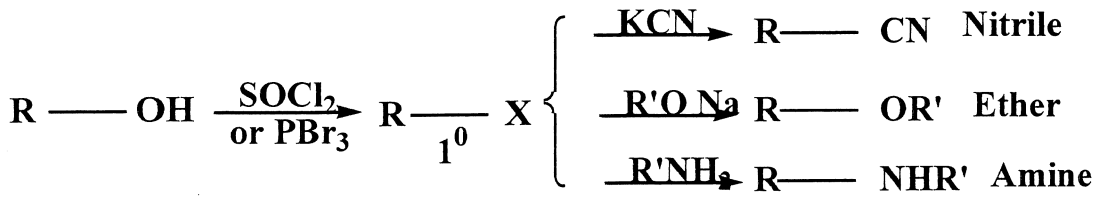
(R)-propylene glycol

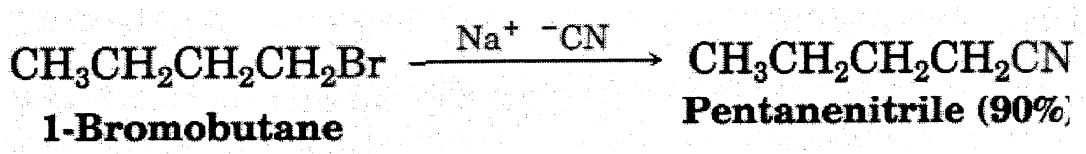
Drug Synthesis
الاصطناع (التخليق) الدوائي

Some types of reactions used in drug synthesis
6. Substitution and elimination reactions

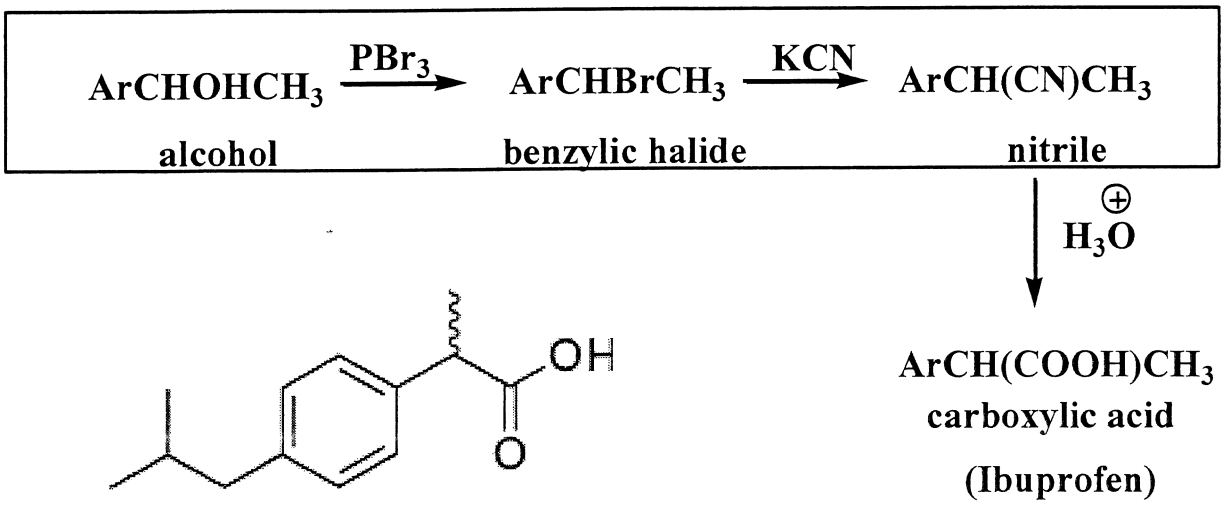
A. Substitution reactions on alcohols and alkyl halides

A. Substitution reactions on alcohols and alkyl halides



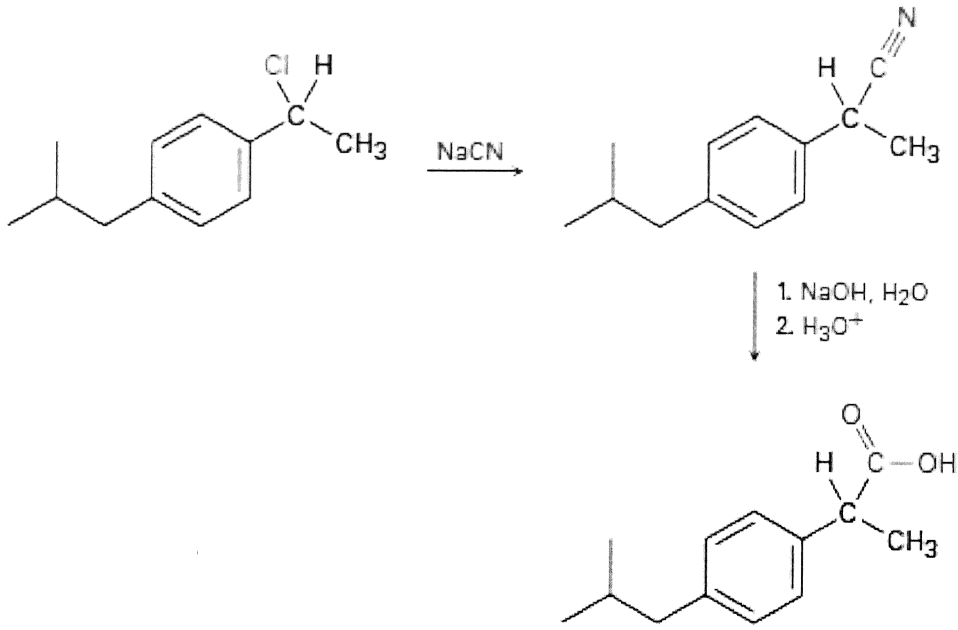


Synthesis of the anti-inflammatory Ibuprofen From Alcohol via Nitrile



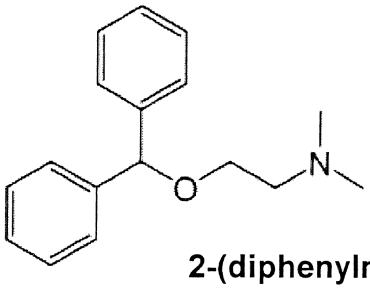
R,S-Ibuprofen

Synthesis of the anti-inflammatory Ibuprofen From Halide via Nitrile



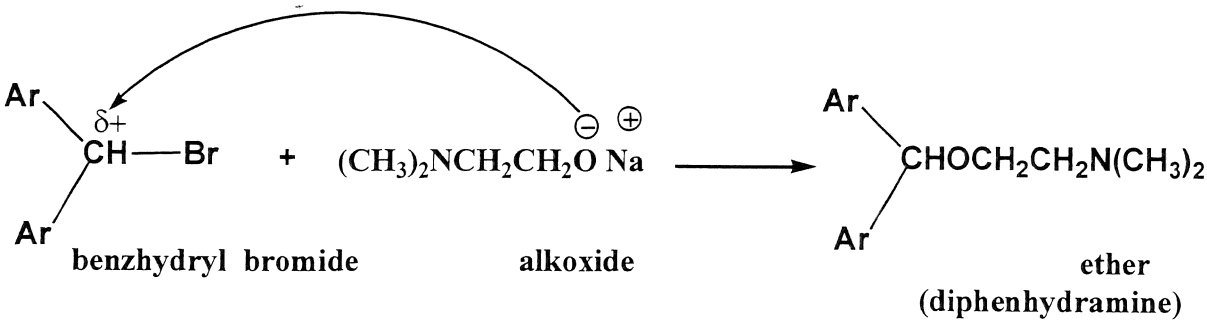
Ibuprofen

Synthesis of aminoalkylethers:Diphenhydramine, (Wiliamson synthesis)

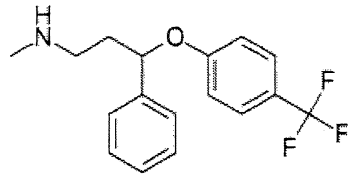


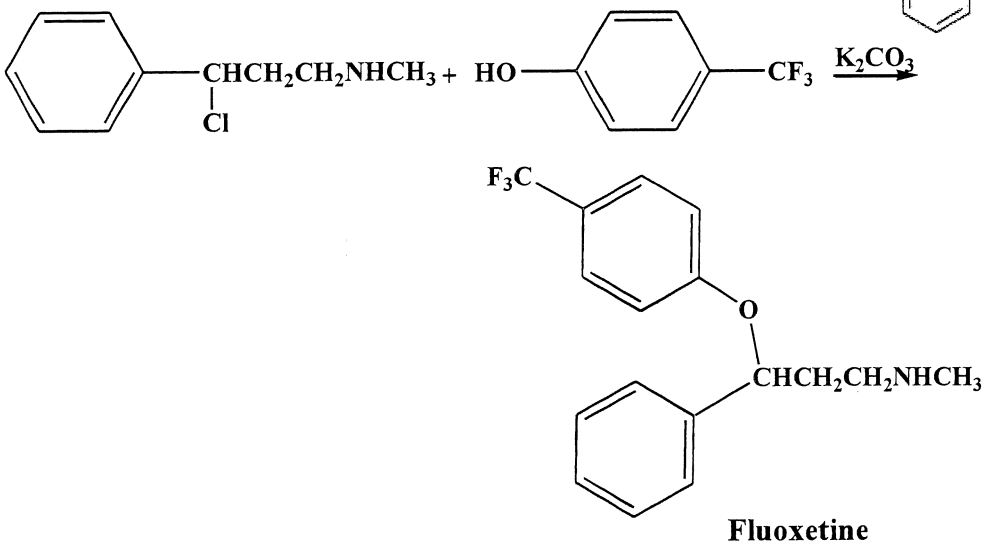
Diphenhydramine

2-(diphenylmethoxy)-*N,N*-dimethylethanamine



Synthesis of the antidepressant aminoalkyl ether Fluoxetine (Wiliamson synthesis)





Fluoxetine

(*RS*)-*N*-methyl-3- phenyl-3- (4-trifluoromethylphenoxy)propan-1-amine

B. Nucleophilic aromatic substitution