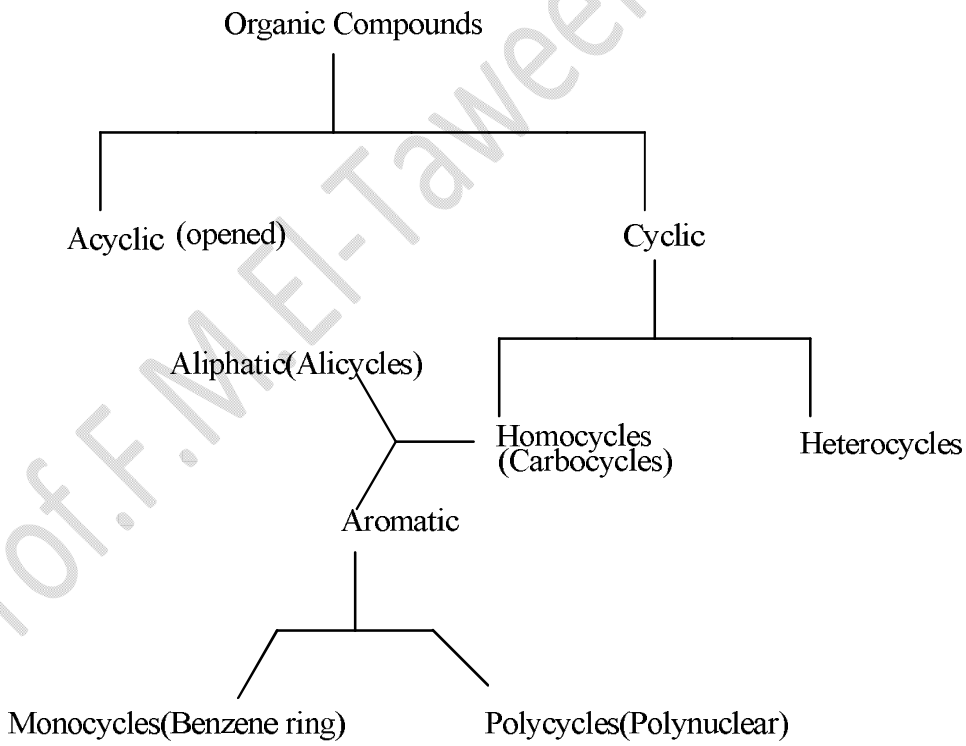
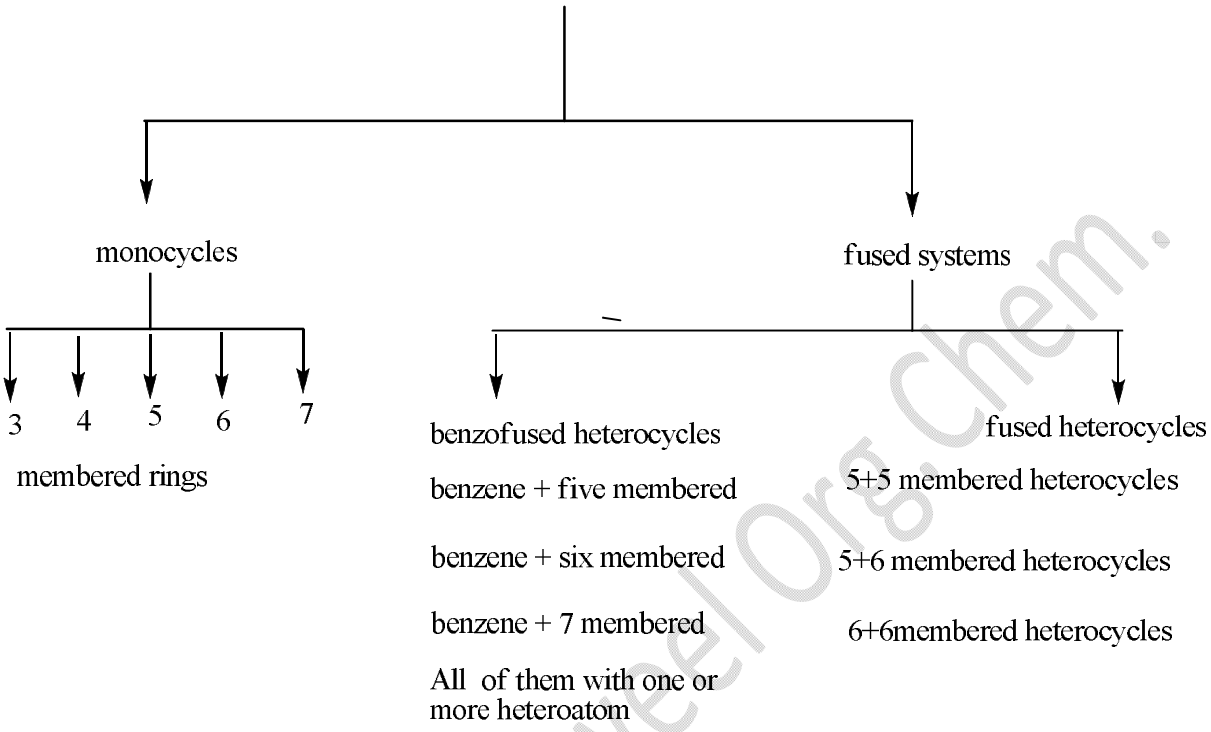
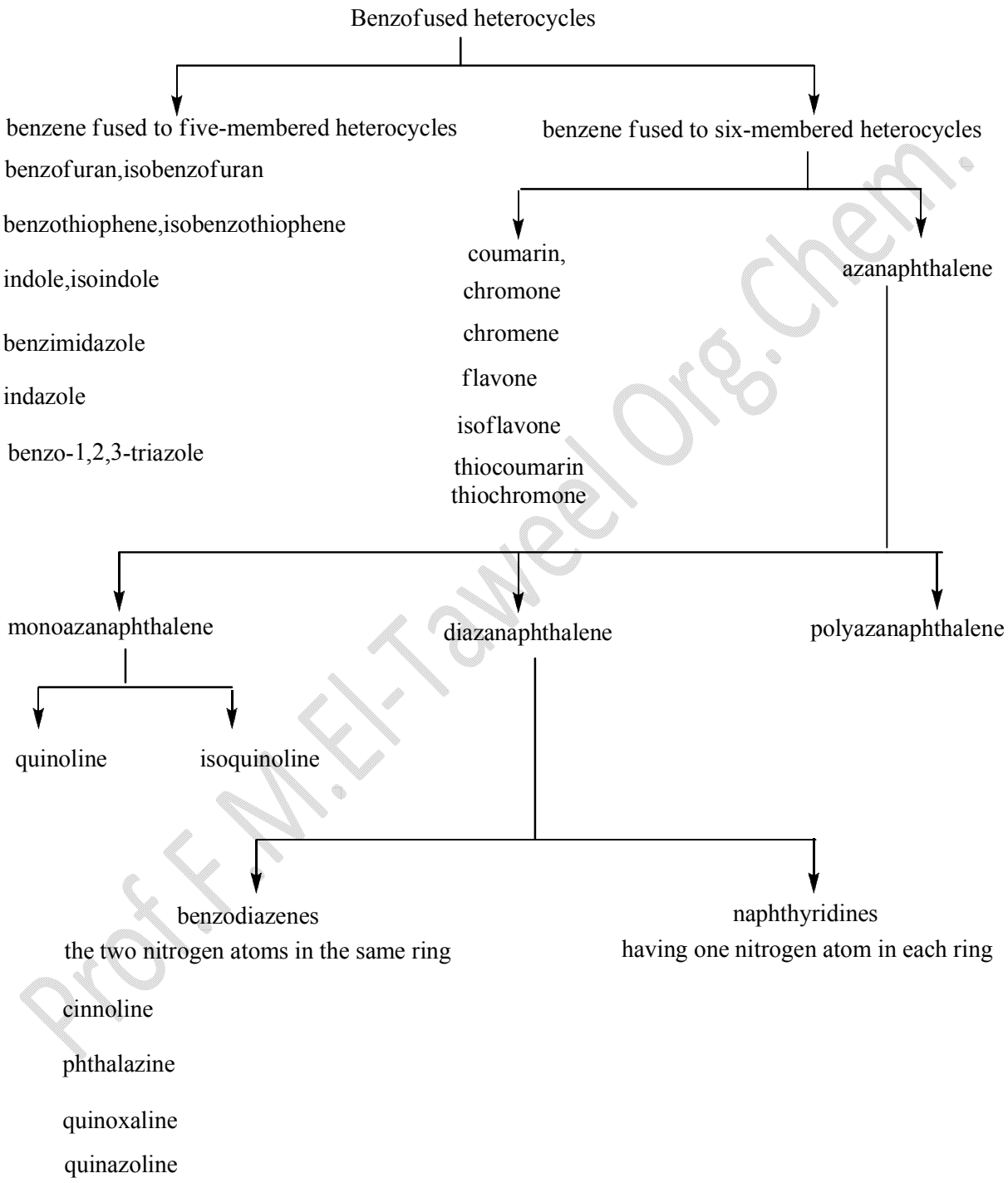


Heterocycles





A)Monoazanapthalenes (Quinoline and Isoquinoline)

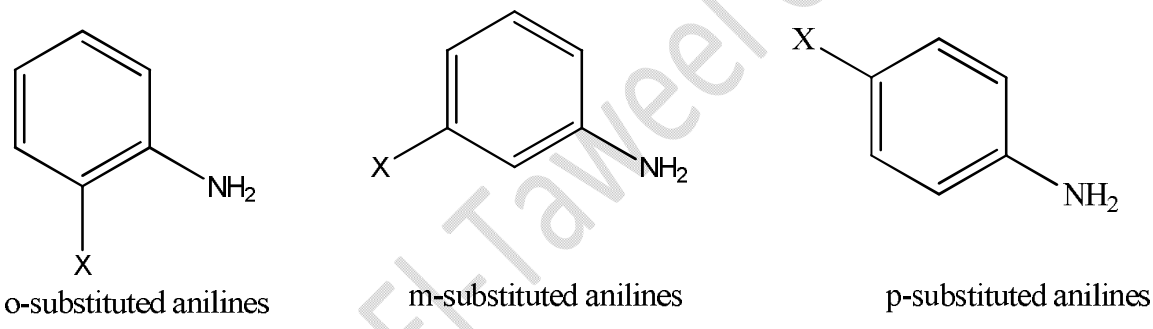
1-*Skraup reaction*:

Consists of heating of primary aromatic amines ($ArNH_2$) e.g.aniline with glycerol,in nitrobenzene (as solvent and oxidizing agent),in presence of $c.H_2SO_4$(as catalyst) and few crystals of $FeSO_4$ (to make the reaction less violent).

If a strong o/p-directing group is present in the m-position e.g.-OCH_3 ,then the 7-substituted quinoline is formed.

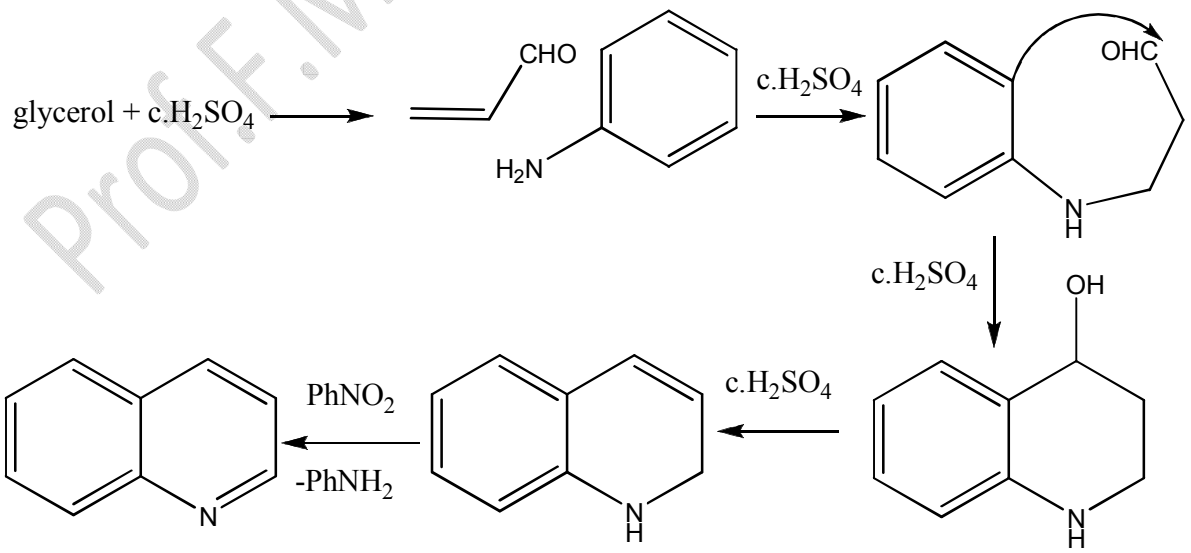
If weakly o/p- directing group is present e.g.Cl,then both 5-and 7- substituted quinolines are formed.

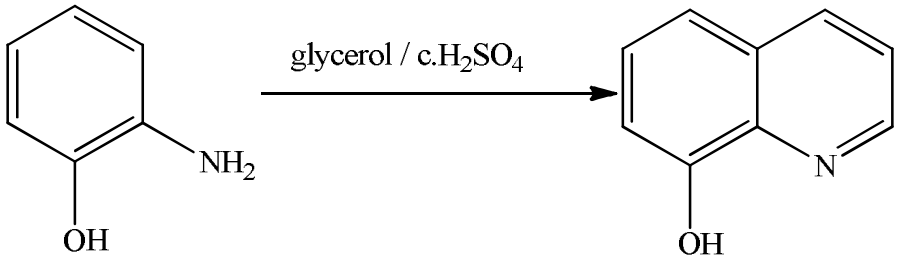
If substitution is m-directing ,the predominant product is the 5-substituted quinoline.



o-substituted anilines m-substituted anilines p-substituted anilines

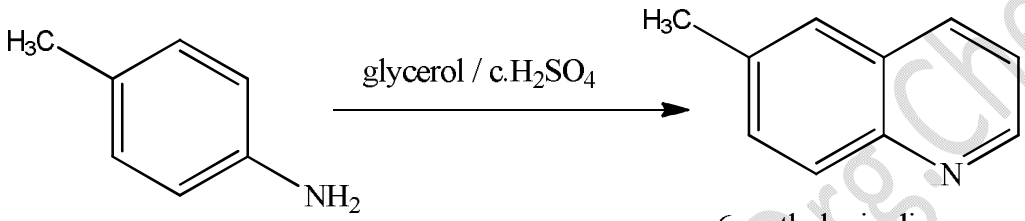
Where is X= R(CH_3,C_2H_5….etc),X(F,Cl.Br,I),OH,-CHO,RCOR,OCH_3, NO_2,CO_2H





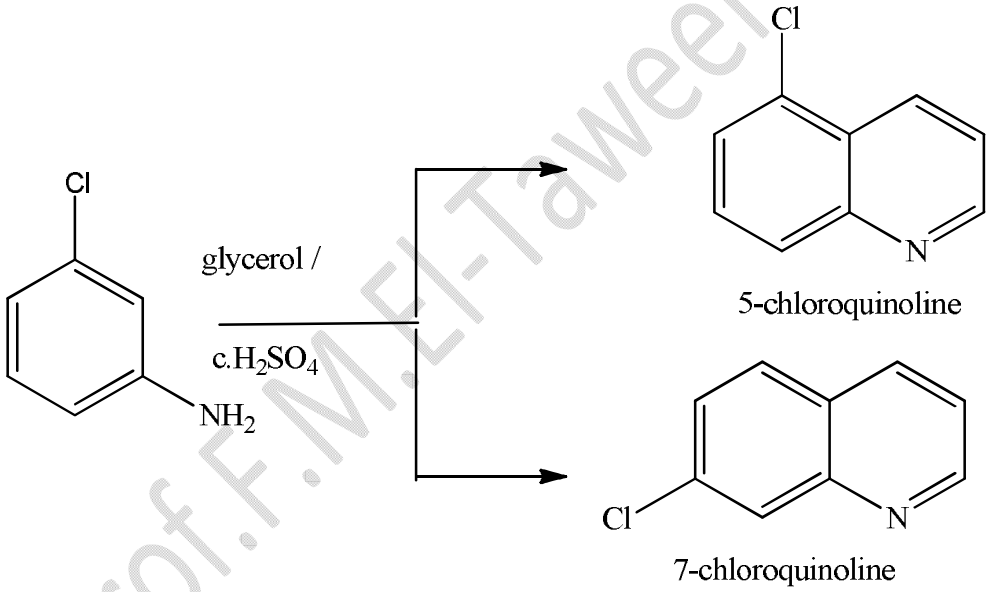
2-aminophenol

8-hyroxyquinoline



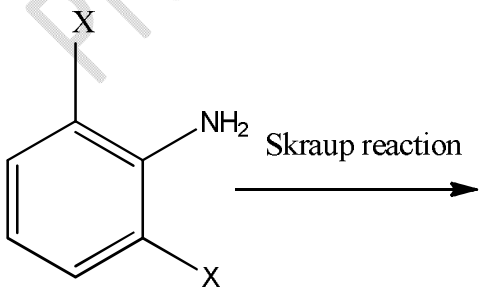
p-toluidine

6-methylquinoline



5-chloroquinoline

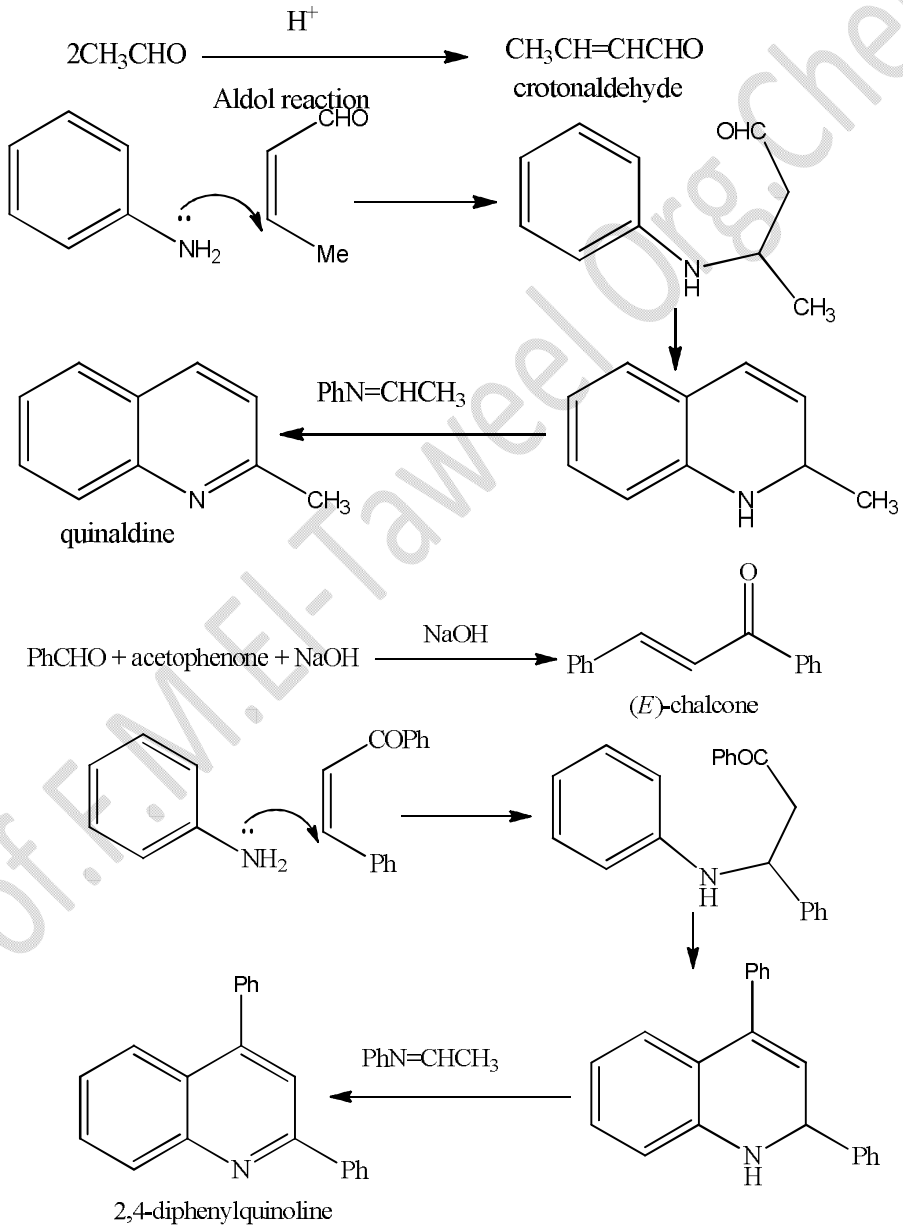
7-chloroquinoline



no reaction due to the fact that 2,6-dichloroaniline hasn't a free position of the NH_2 group

2- **Doebner - Miller reaction**:

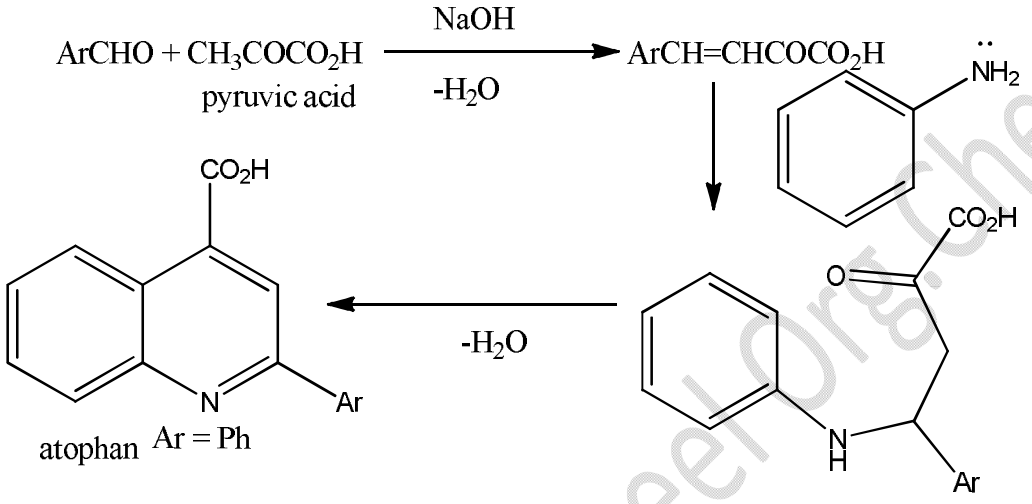
In this case α,β-unsaturated aldehydes or ketones are used in place of glycerol,thus,there is therefore a greater variation in the possible substitution pattern and HCl or ZCl_2 is used as a catalyst.Also,primary aromatic amines are used.



We also can use o-,m-,and p-substituted anilines.

3- ***Doebner reaction***:

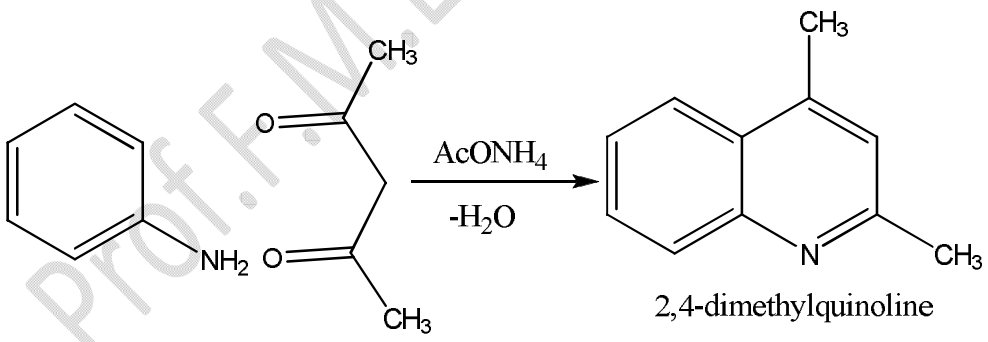
Formation of substituted cinchoninic acid from aromatic amines on heating with aldehydes and pyruvic acid.

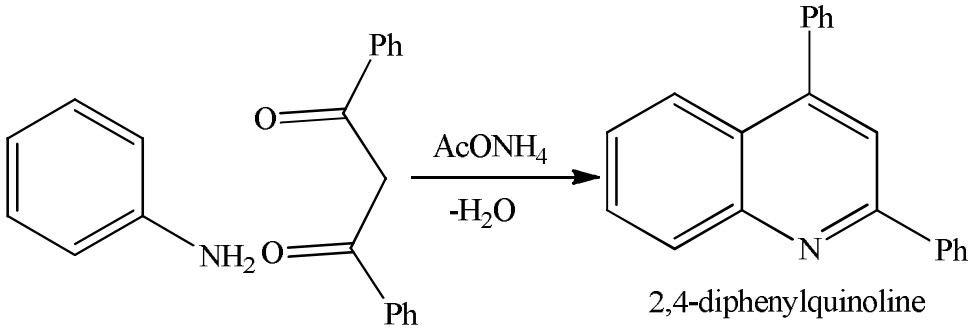


We also can use o-,m-,and p-substituted anilines

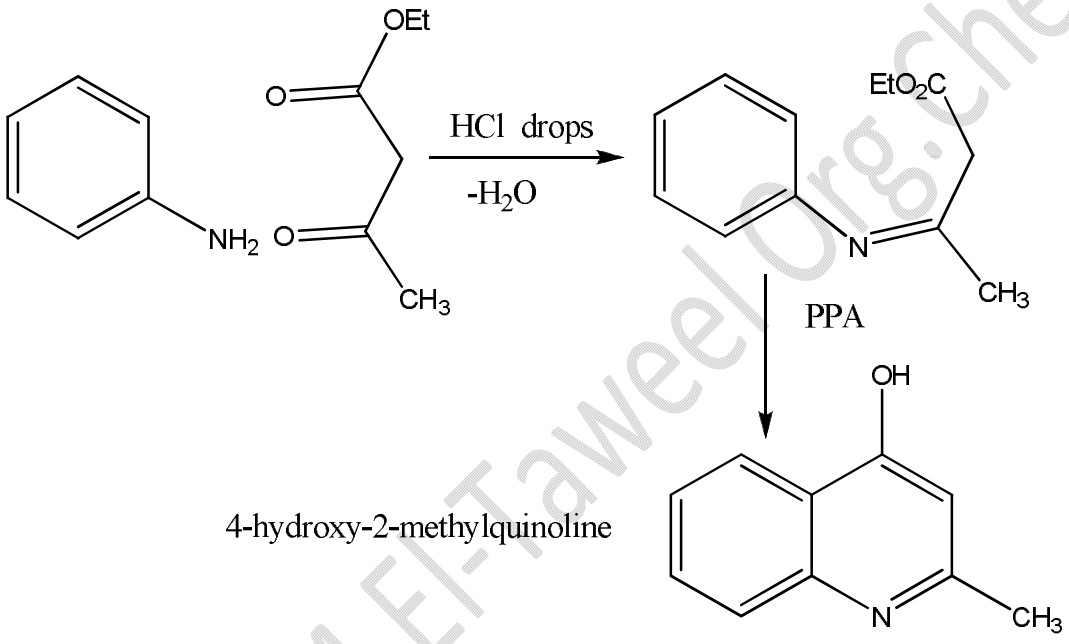
4- ***Combes reaction***:

Condensation of $ArNH_2$ with 1,3-dicarbonyl compounds (β-ketoesters or β-diketones).

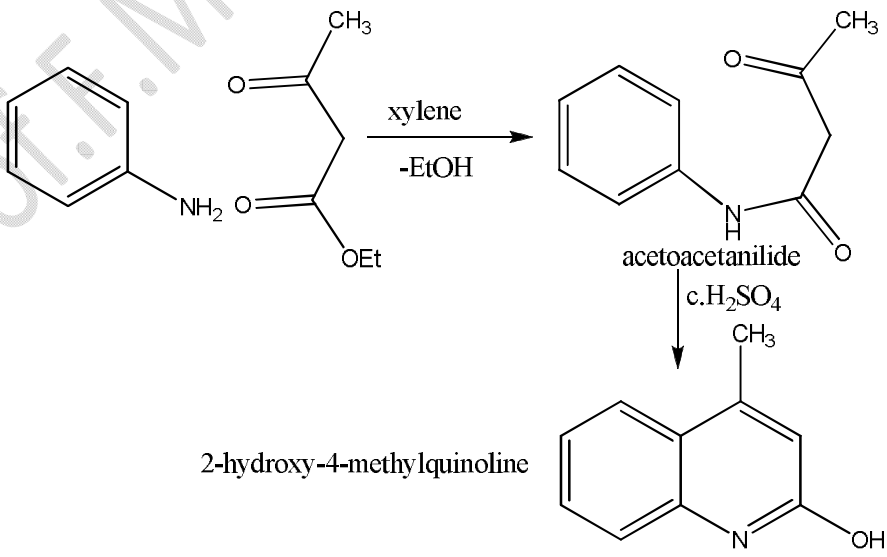




2,4-diphenylquinoline

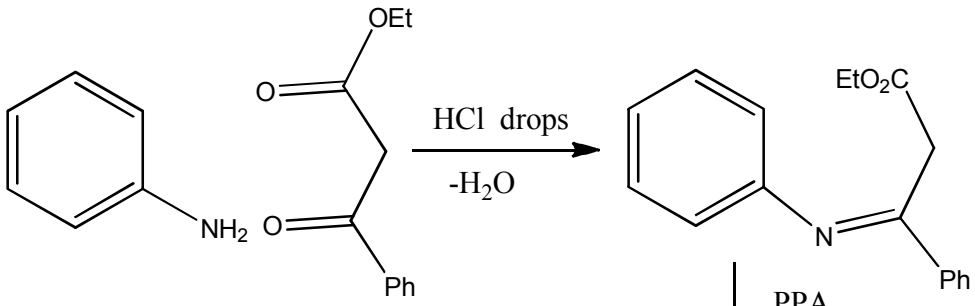


4-hydroxy-2-methylquinoline

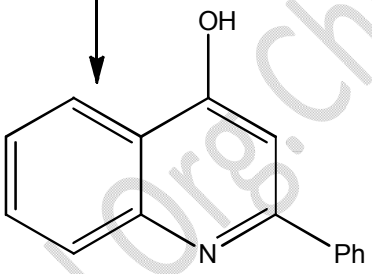


acetoacetanilide

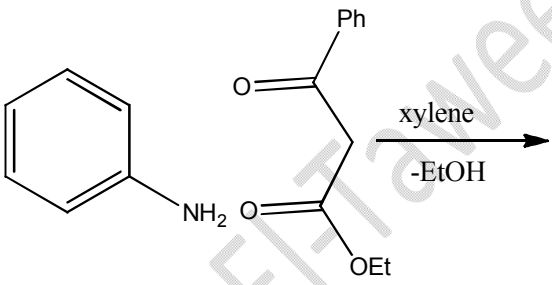
2-hydroxy-4-methylquinoline



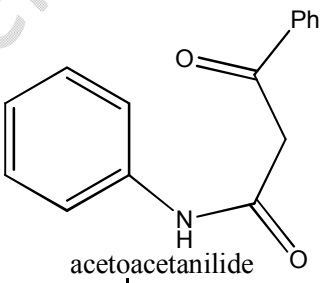
PPA



2-phenylquinolin-4-ol

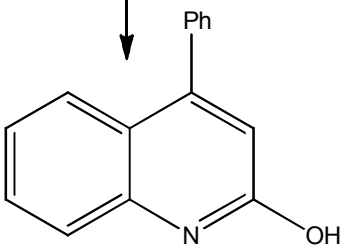


ethyl benzoylacetate

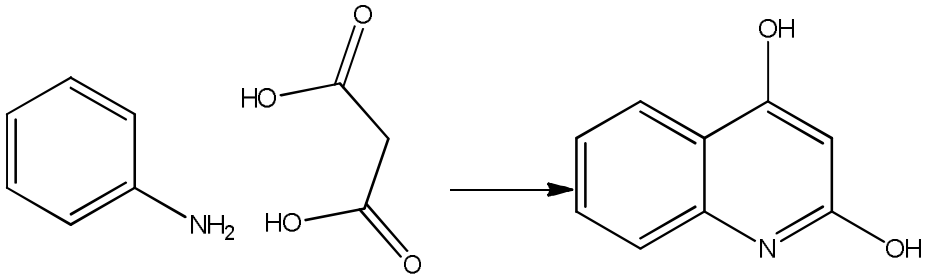


acetoacetanilide

$c.H_2SO_4$



4-phenylquinolin-2-ol



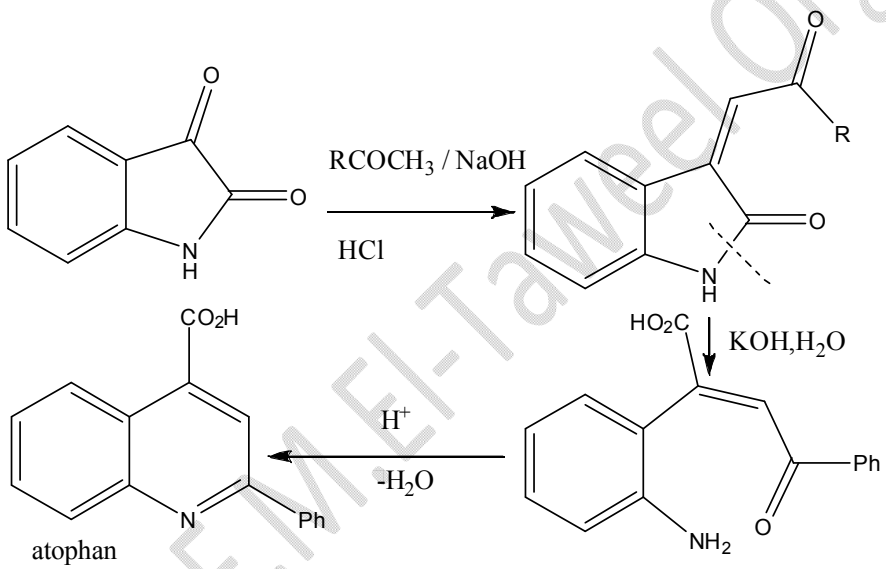
malonic acid

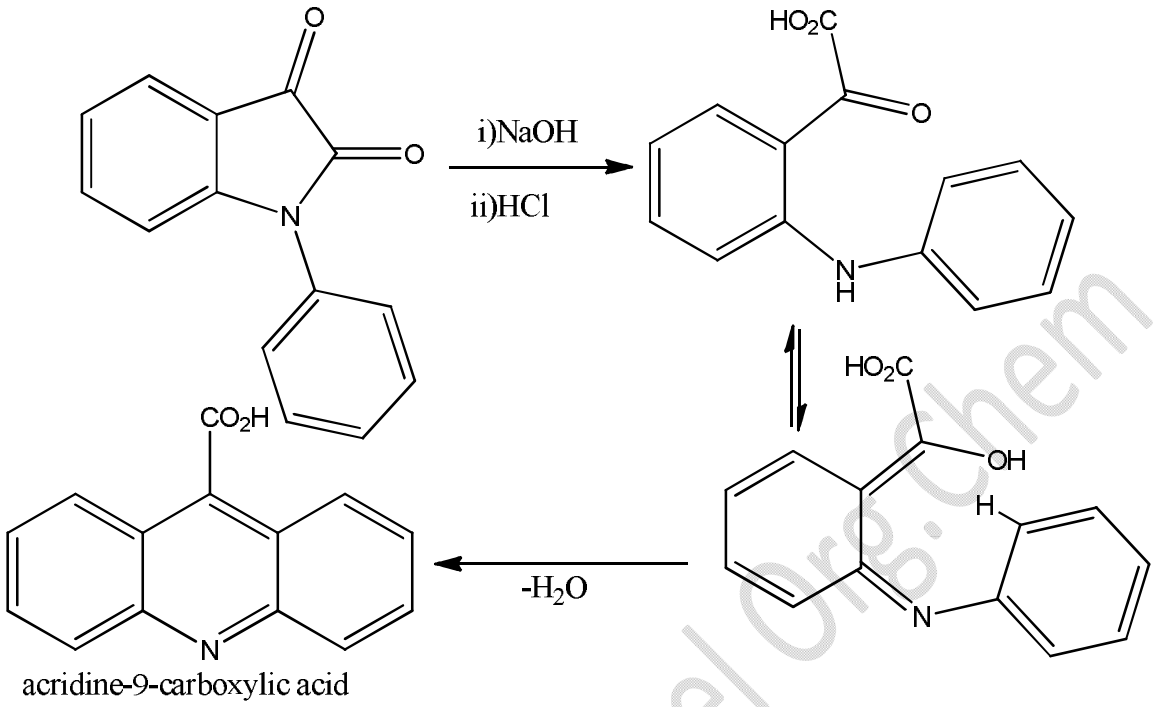
or diethyl malonate

quinoline-2,4-diol

5- **Pfitzinger reaction**:

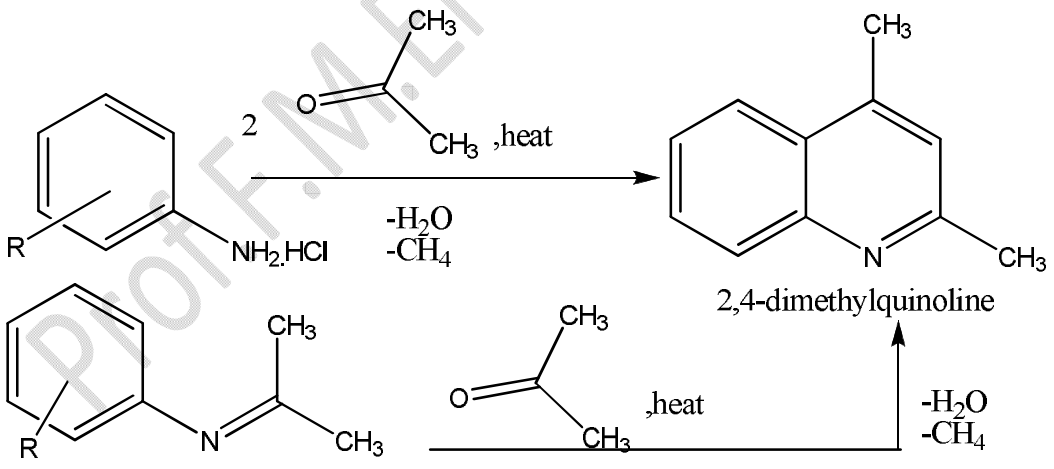
Condensation of acylketones with isatin,then after hydrolysis yield quinoline-4-carboxylic acid.

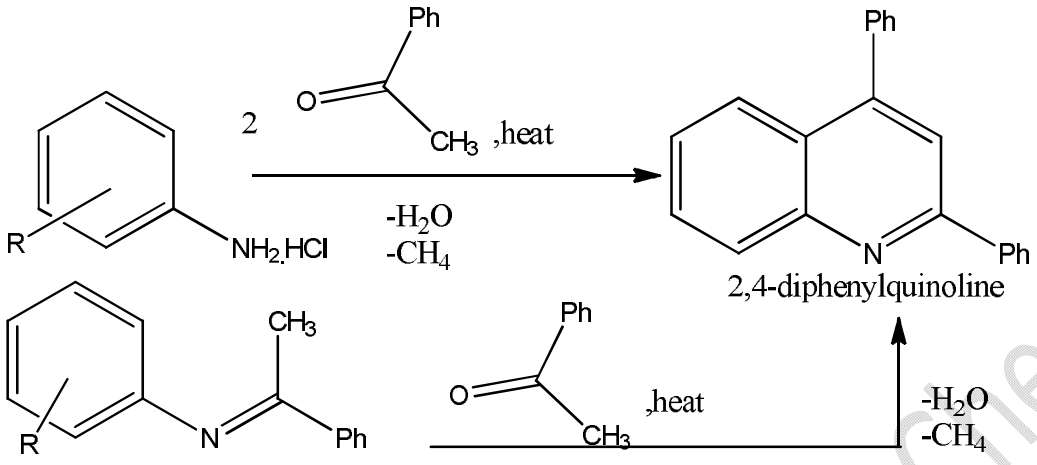




6- **Riehm reaction**:

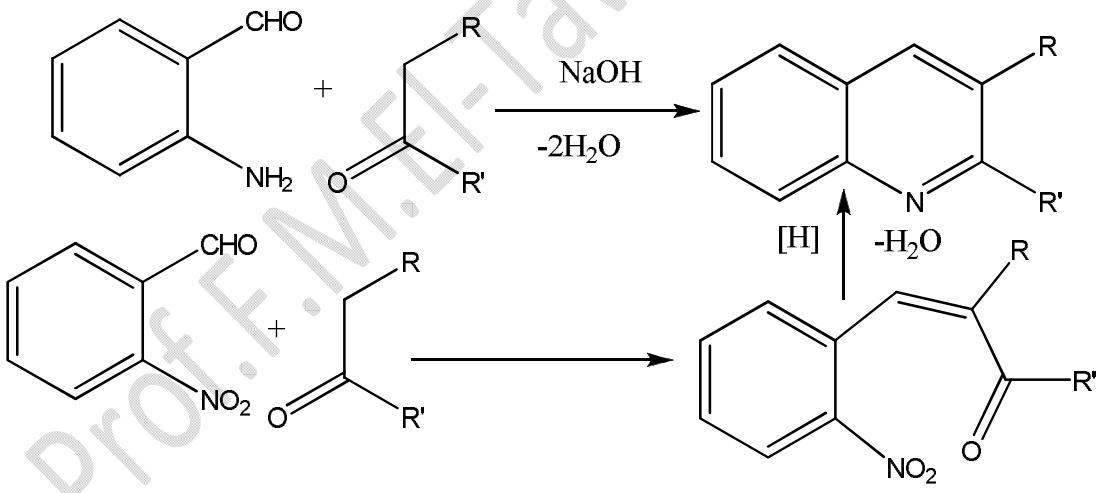
Formation of quinoline derivatives by prolonged heating of primary arylamine hydrochlorides with ketones with or without use of $AlCl_3$ or PCl_5(Lewis acid catalyst).



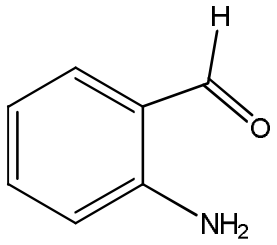


7-**Friedlander synthesis :**

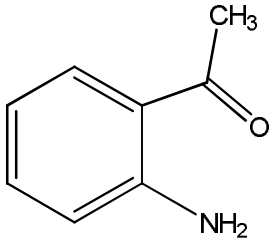
Such a reaction in which an o-aminoaldehydes or o-aminoketones can be cyclised by reaction with an α-methylenealdehyde or α-methyleneketone or a related compounds in the presence of a base .Its synthetic used is limited by the difficulty in preparing the o-aminocarbonyl compounds.



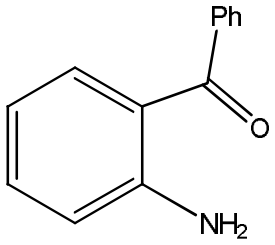
The following o-aminoaldehydes and o-aminoketones can be used for preparation of quinoline derivatives.



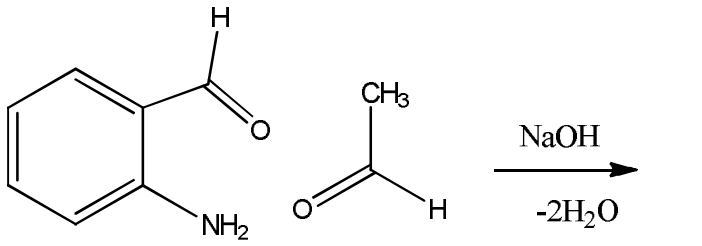
2-aminobenzaldehyde



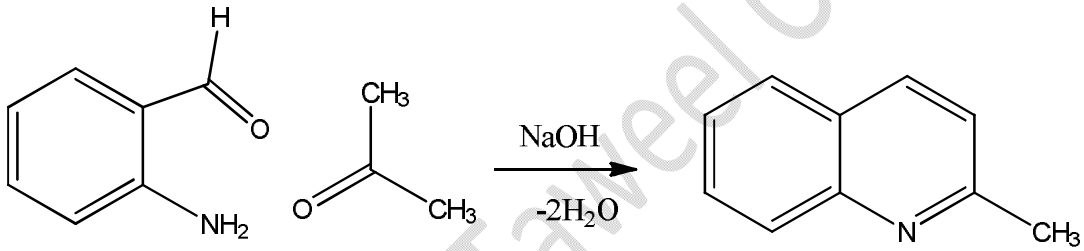
1-(2-aminophenyl)ethanone



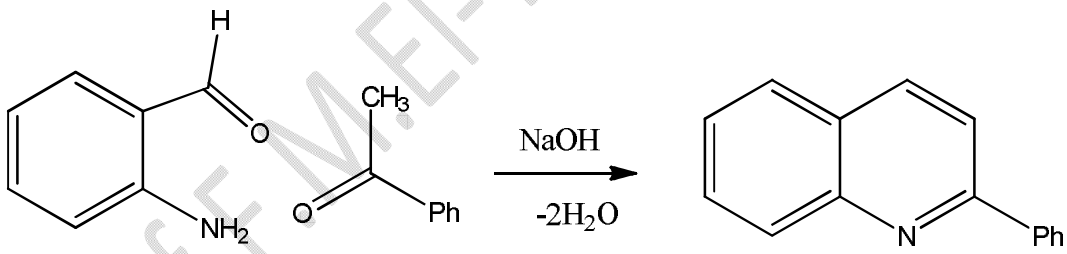
(2-aminophenyl)(phenyl)methanone



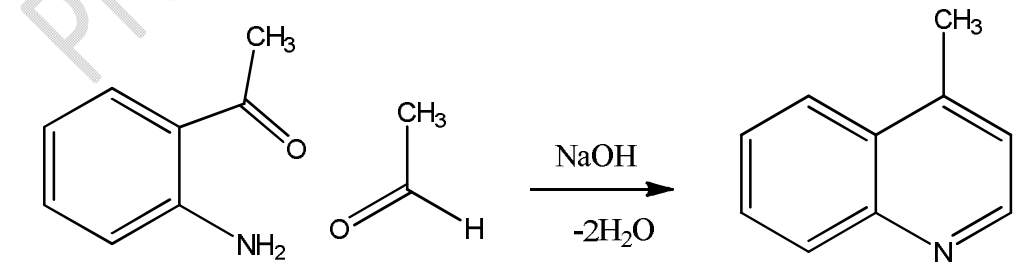
2-aminobenzaldehyde quinoline



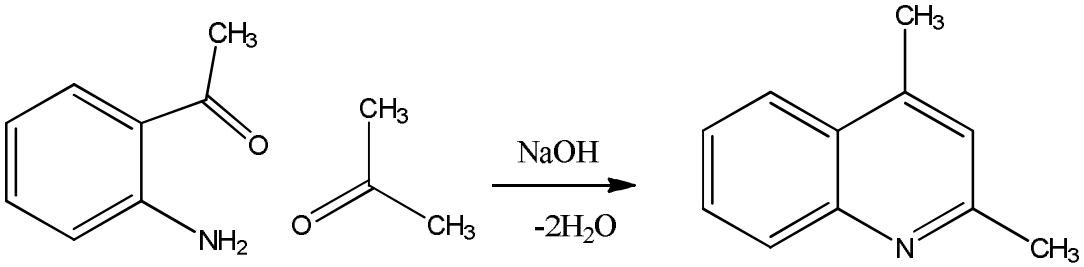
2-aminobenzaldehyde 2-methylquinoline



2-aminobenzaldehyde 2-phenylquinoline

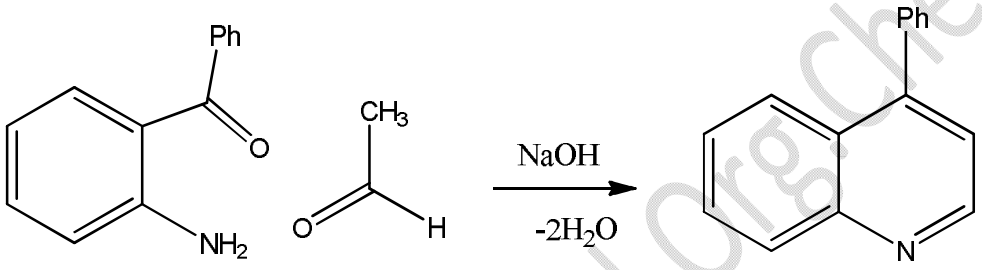


1-(2-aminophenyl)ethanone 4-methylquinoline



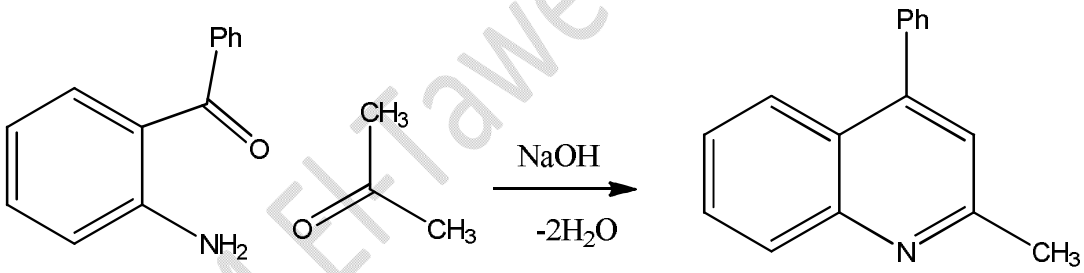
1-(2-aminophenyl)ethanone

2,4-dimethylquinoline



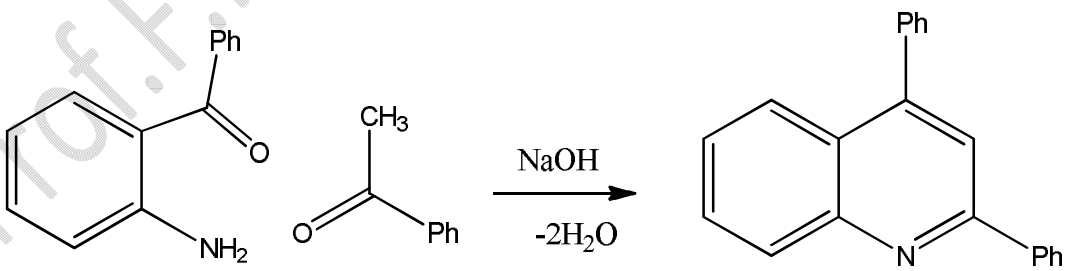
(2-aminophenyl)(phenyl)methanone

4-phenylquinoline



(2-aminophenyl)(phenyl)methanone

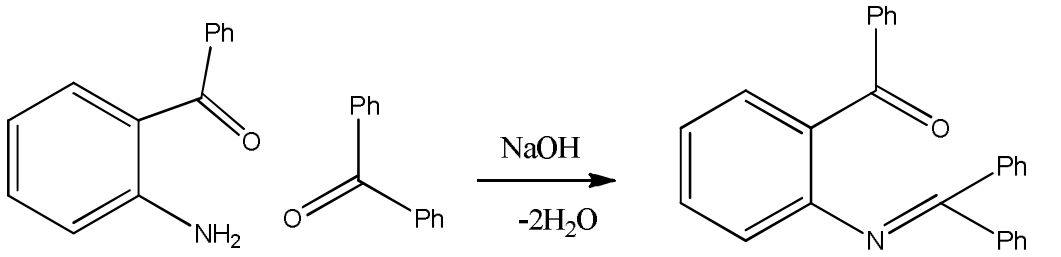
2-methyl-4-phenylquinoline



(2-aminophenyl)(phenyl)methanone

2,4-diphenylquinoline

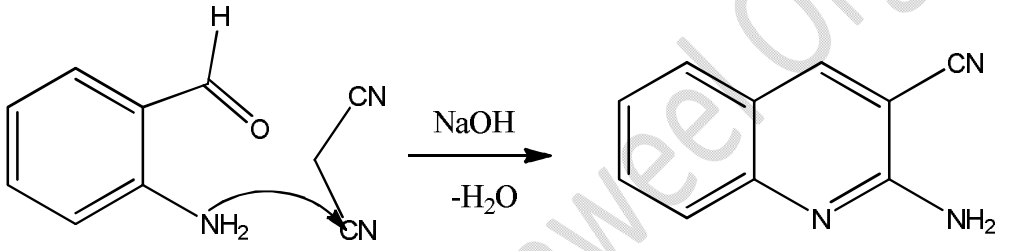
In the following equation ,there is no Skraup reaction,



(2-aminophenyl)(phenyl)methanone

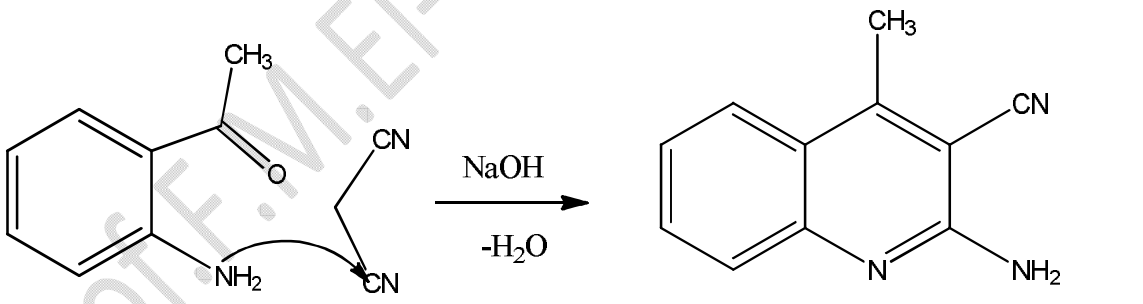
(2-((diphenylmethylene)amino)phenyl)(phenyl) methanone

Quinoline derivatives can be prepared by reacting ethyl acetoacetate ,ethyl benzoylacetate ,acetylacetone and dibenzoylmethane with the above o-aminoaldehydes or o-aminoketones and dicyanomethane (malononitrile) .



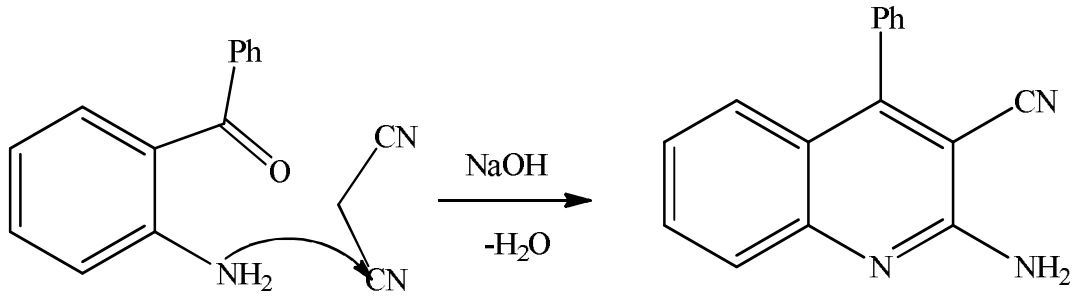
2-aminobenzaldehyde

2-aminoquinoline-3-carbonitrile



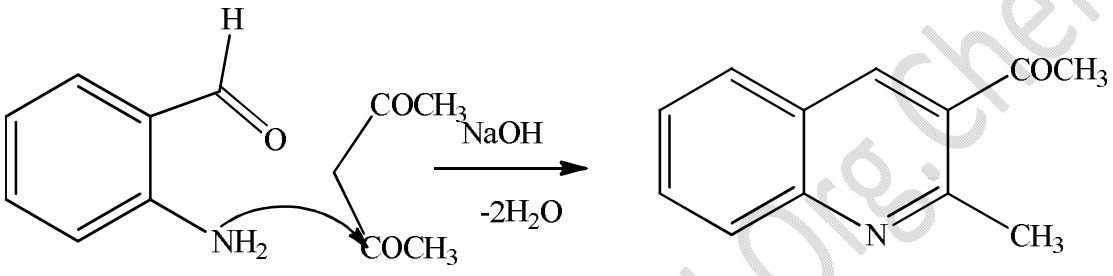
1-(2-aminophenyl)ethanone

2-amino-4-methylquinoline-3-carbonitrile



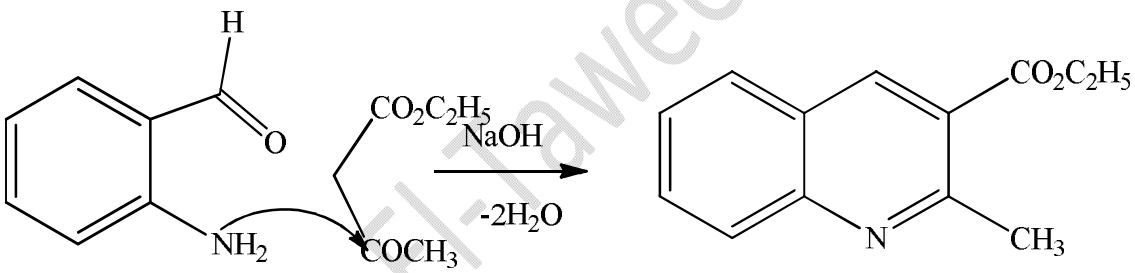
(2-aminophenyl)(phenyl)methanone

2-amino-4-phenylquinoline-3-carbonitrile



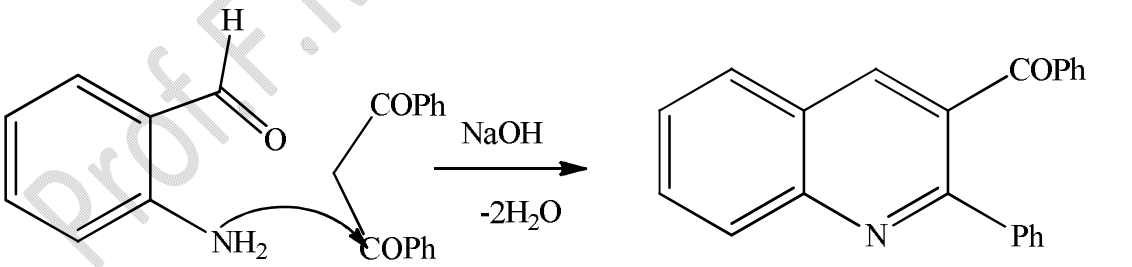
2-aminobenzaldehyde

1-(2-methylquinolin-3-yl)ethanone



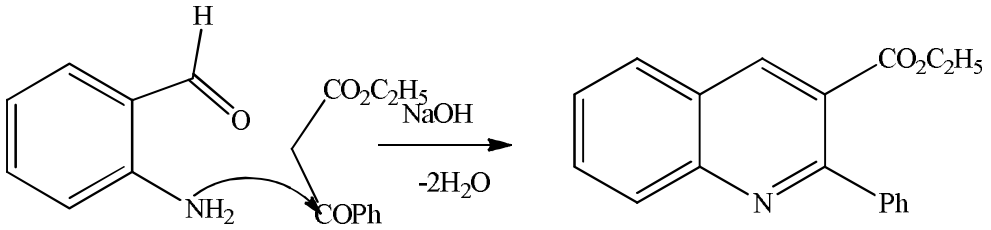
2-aminobenzaldehyde

ethyl 2-methylquinoline-3-carboxylate

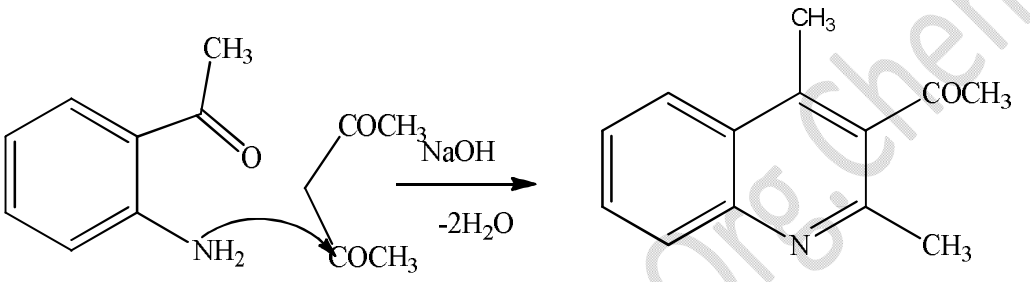


2-aminobenzaldehyde

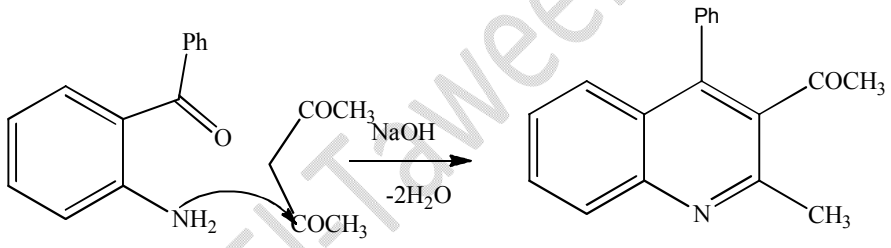
phenyl(2-phenylquinolin-3-yl)methanone



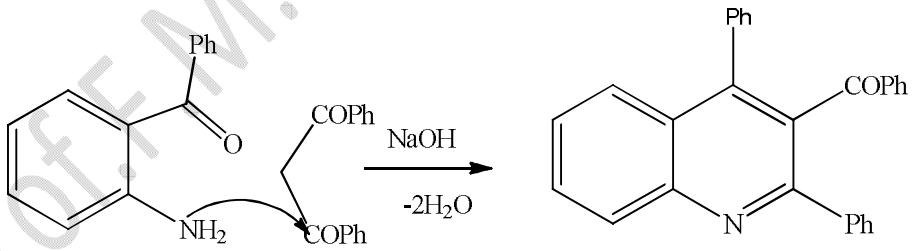
2-aminobenzaldehyde ethyl 2-phenylquinoline-3-carboxylate



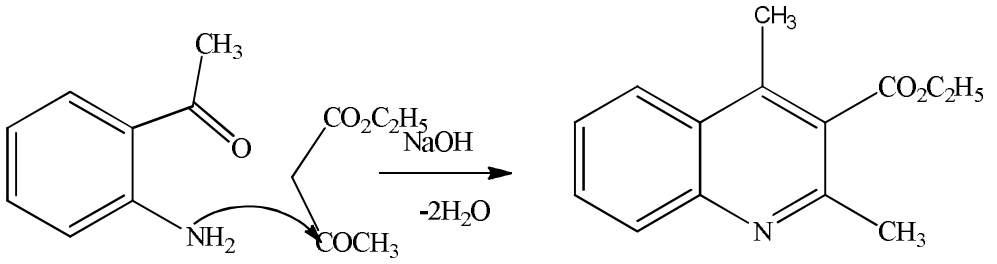
1-(2-aminophenyl)ethanone 1-(2,4-dimethylquinolin-3-yl)ethanone



(2-aminophenyl)(phenyl)methanone 1-(2-methyl-4-phenylquinolin-3-yl)ethanone

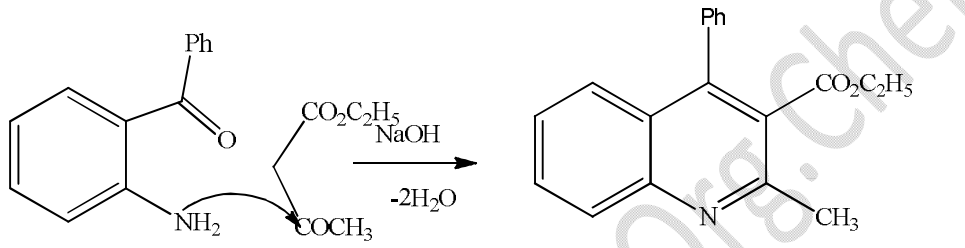


(2-aminophenyl)(phenyl)methanone (2,4-diphenylquinolin-3-yl)(phenyl)methanone



1-(2-aminophenyl)ethanone

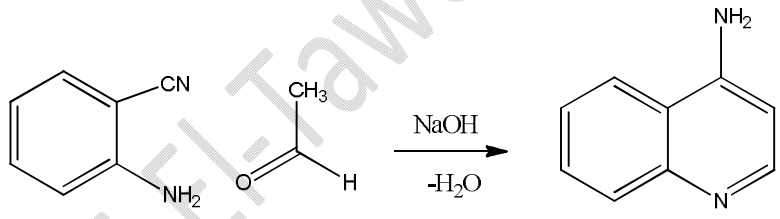
ethyl 2,4-dimethylquinoline-3-carboxylate



(2-aminophenyl)(phenyl)methanone

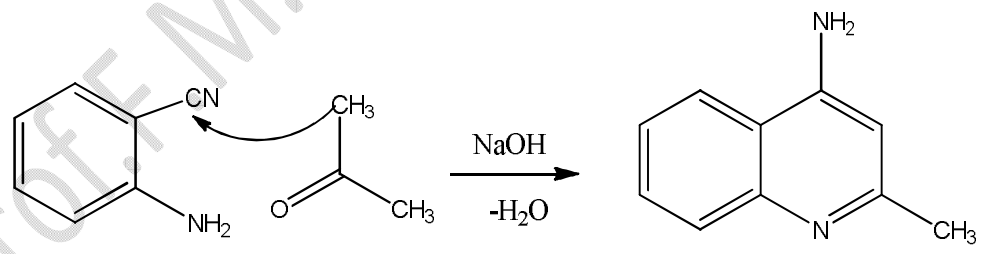
ethyl 2-methyl-4-phenylquinoline-3-carboxylate

2-Cyanoaniline can be used for preparation of quinoline derivatives using the same reactants under the same conditions.



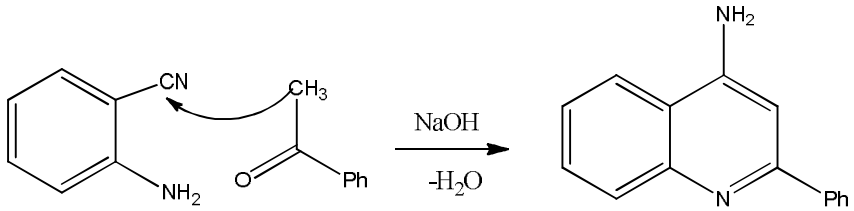
2-aminobenzonitrile

quinolin-4-amine



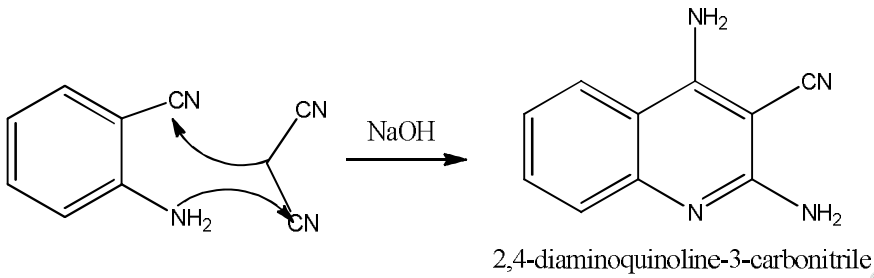
2-aminobenzonitrile

2-methylquinolin-4-amine

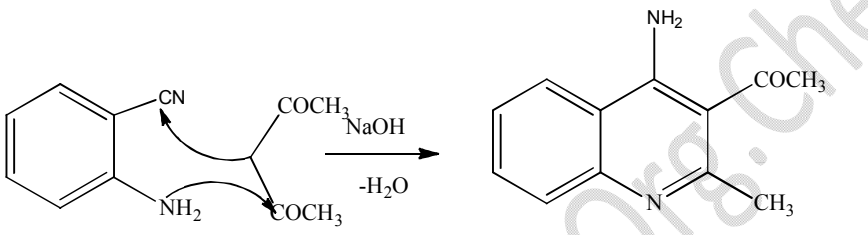


2-aminobenzonitrile

2-phenylquinolin-4-amine

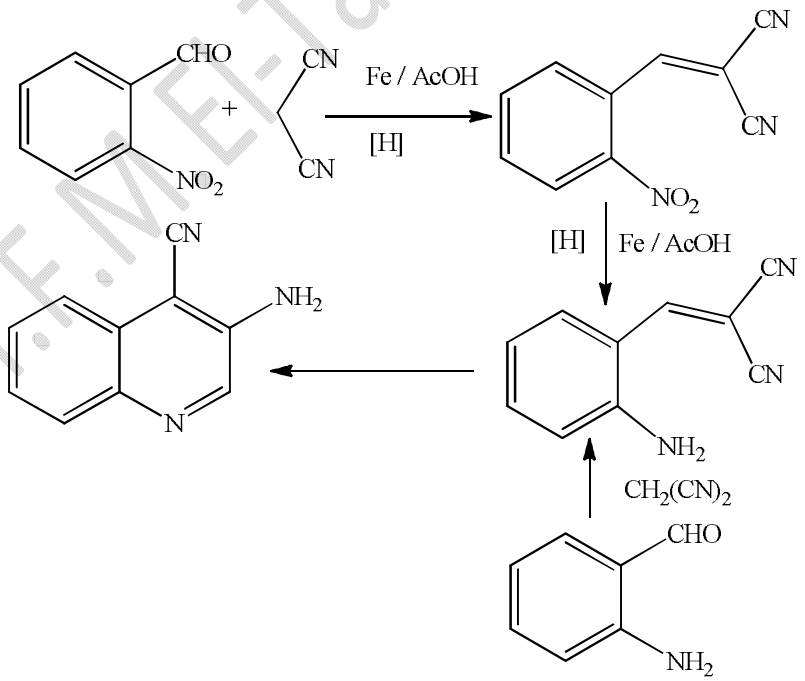


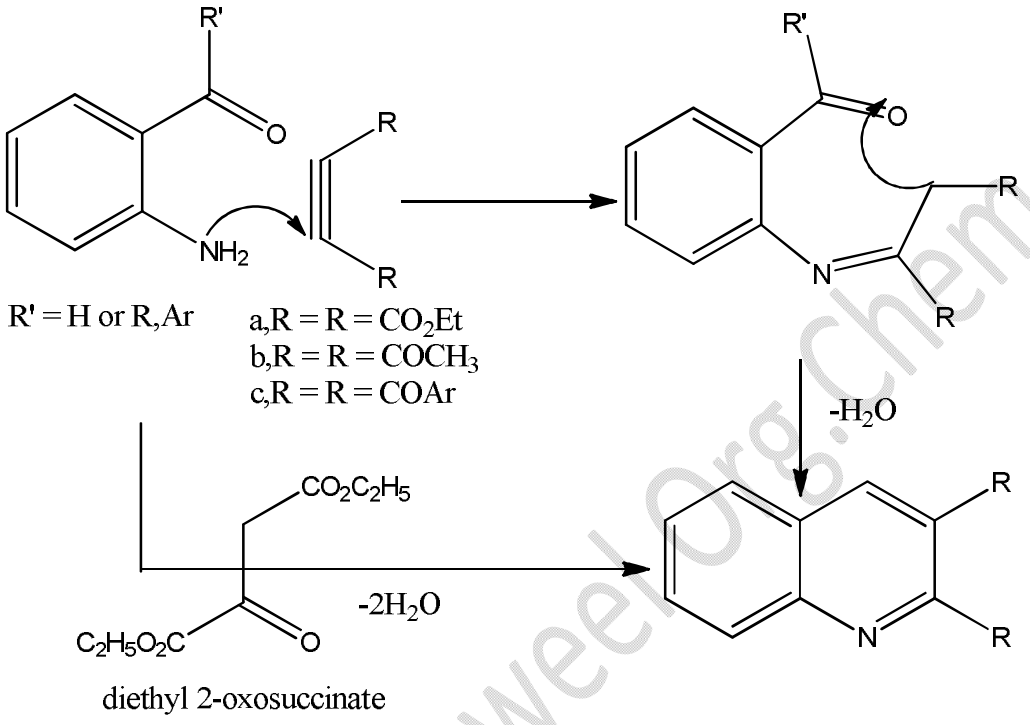
2,4-diaminoquinoline-3-carbonitrile



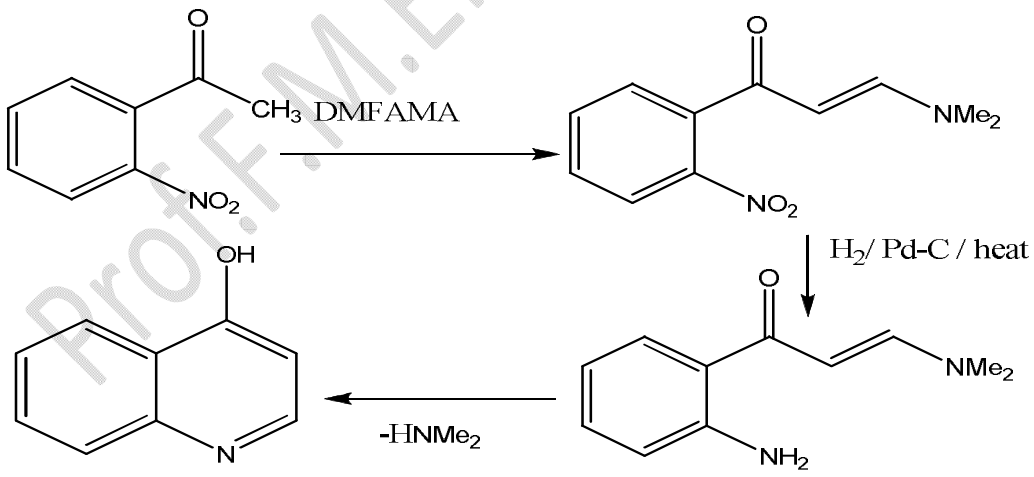
1-(4-amino-2-methylquinolin-3-yl)ethanone

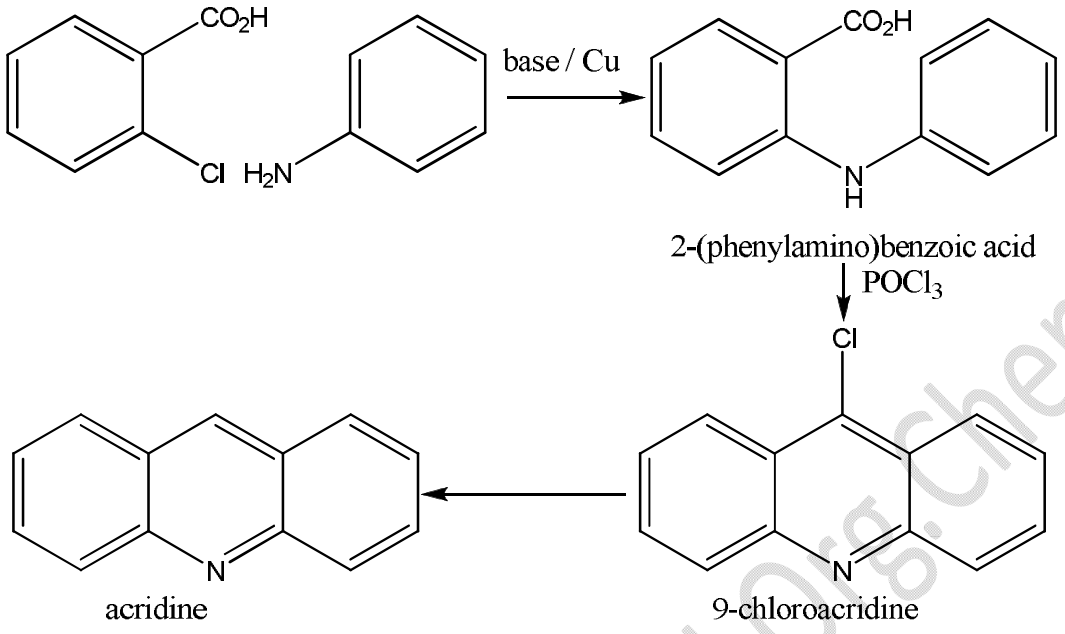
A useful modification is the reaction of an o-nitrocarbonyl compounds with activated methylene and subsequent reduction of the nitro group as shown above and below.





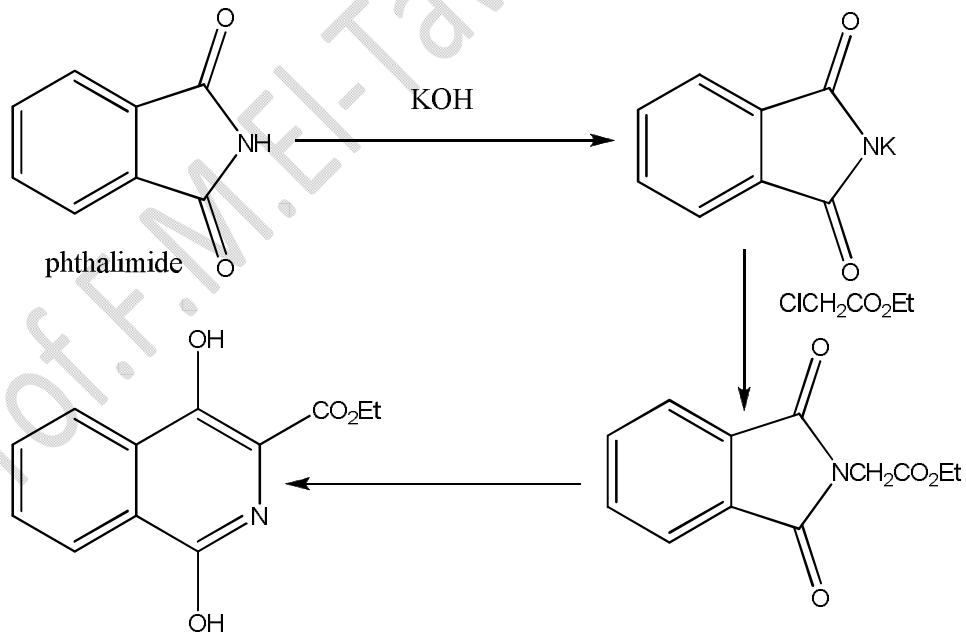
Other methods :



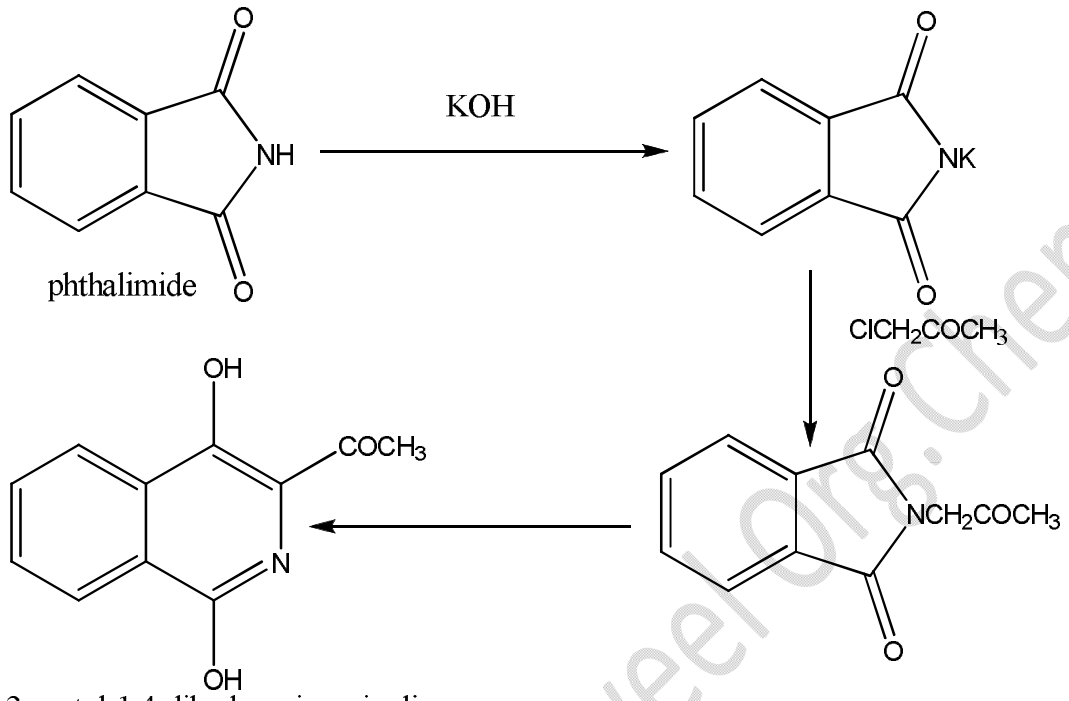


Gabriel-Colmann rearrangement :

Formation of isoquinoline derivatives by the action of EtONa Phalimidoacetic ester.

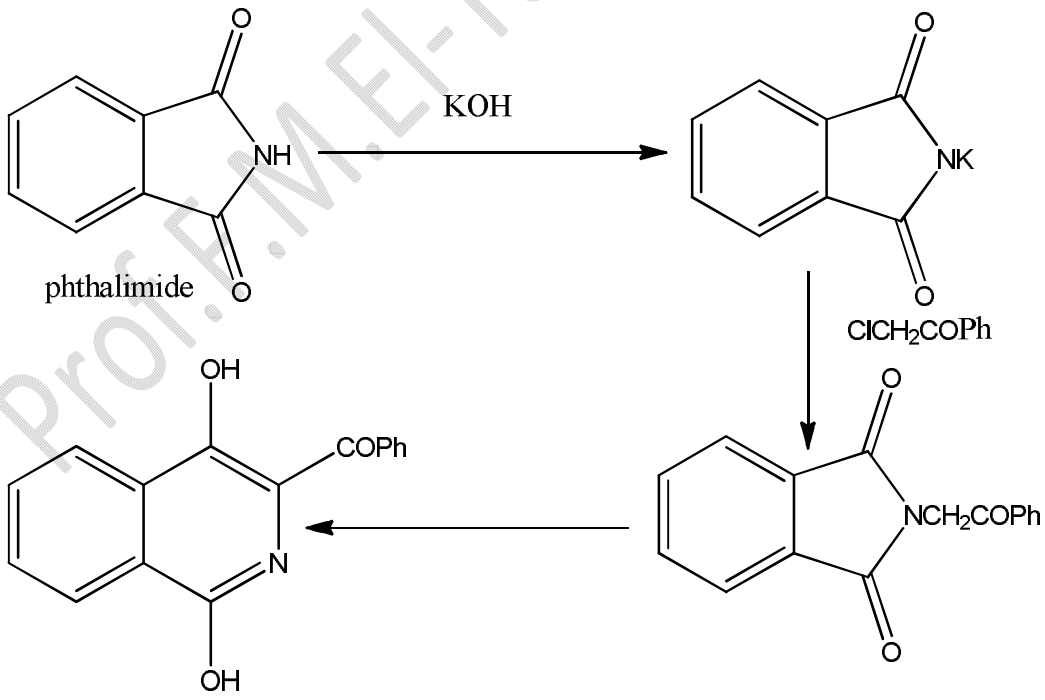


Also,



3-acetyl-1,4-dihydroxyisoquinoline

Also,

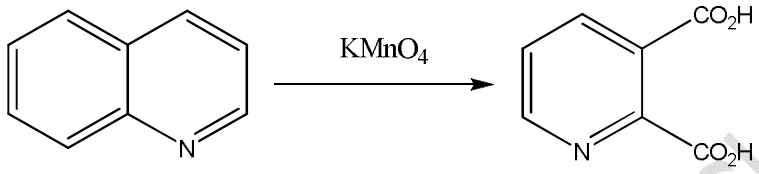


(1,4-dihydroxyisoquinolin-3-yl)(phenyl)methanone

Reactions with quinoline :

a-**Oxidation**:

Quinoline is resistant to oxidizing agents , but vigorous oxidation with $KMnO_4$ yields quinolinic acid.



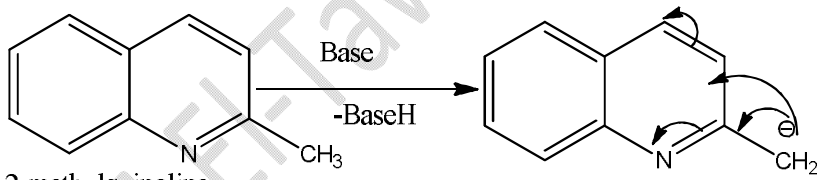
pyridine-2,3-dicarboxylic acid

Reactivity of methyl groups in quinoline and iso quinoline.

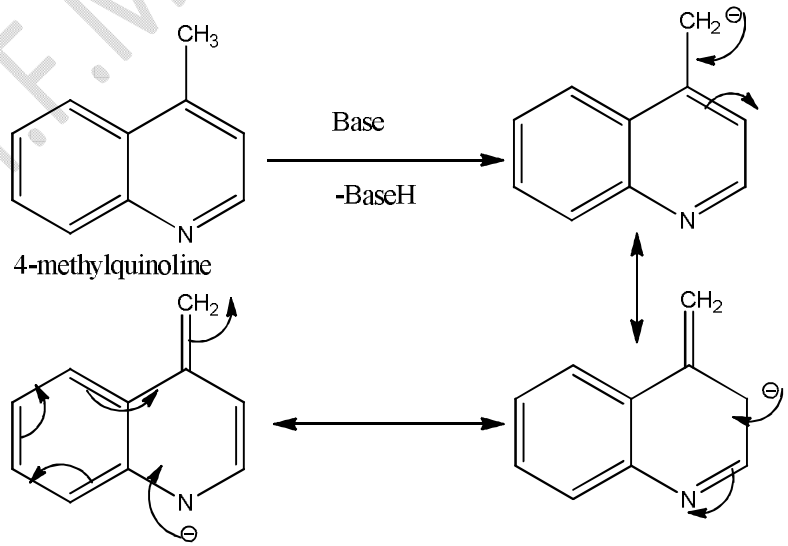
The reactivity of methyl groups in the 2- and 4- positions are typical of these azines and their benzo derivatives.

Also,it has been found that,4-methylquioline and 2-methylquinazoline are reactive.

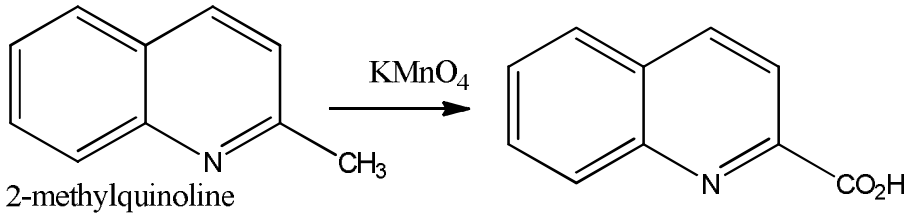
Also ,the methyl group at C-1 in isoquinoline is active.



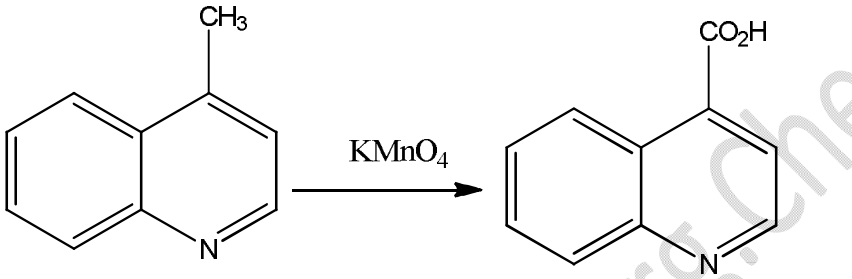
2-methylquinoline



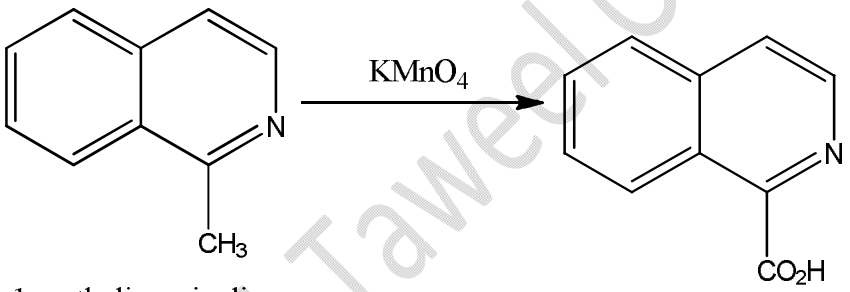
4-methylquinoline



2-methylquinoline



4-methylquinoline quinoline-4-carboxylic acid



1-methylisoquinoline isoquinoline-1-carboxylic acid

c-**Electrophilic substitution**:

Quinoline undergoes electrophilic substitution ,.e.g.nitration , sulphontion and halogenations .As the nitrogen atom deactivates the pyridine ring , electrophilic substitution occurs in the benzene ring (at position-5 and 8).Position -8 is more preferred.