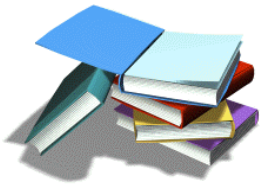
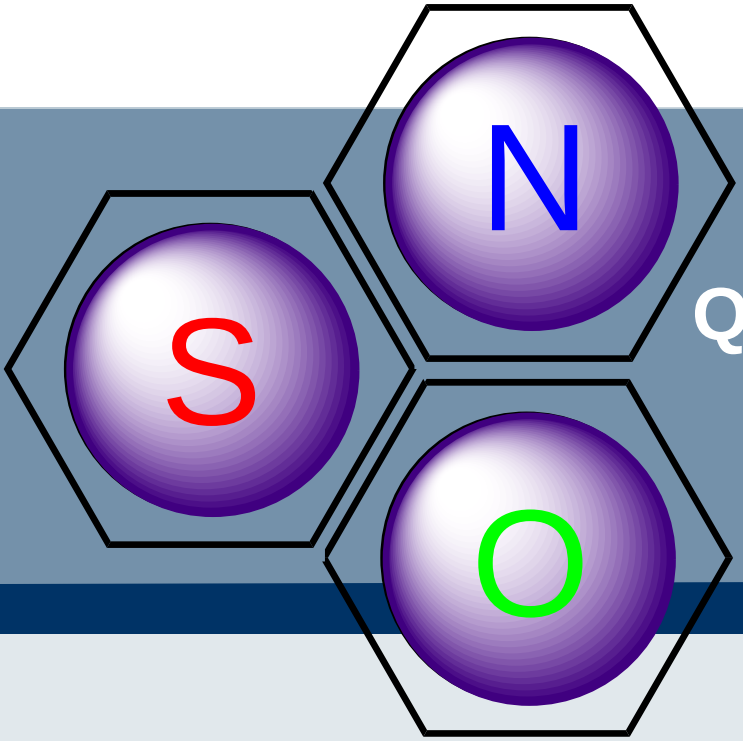
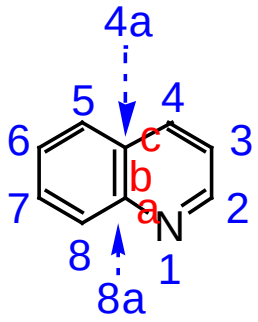


Chapter 7

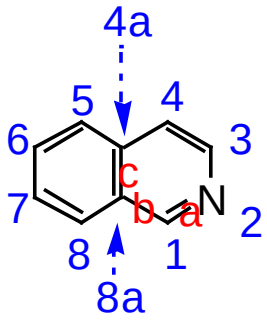


Quinolines and Isoquinolines

BENZO CONDENSED PYRIDINES: QUINOLINES AND ISOQUINOLINES



Quinoline
Benzo[b]pyridine
(1-azanaphtalene)



Isoquinoline
Benzo[c]pyridine
(2-azanaphtalene

Quinoline is a high-boiling liquid; isoquinoline is a low - melting solid; each has a sweetish odour. Both bases have been known for a long time: quinoline was first isolated from coal tar in 1834, isoquinoline from the same source in 1885. Shortly after the isolation of quinoline from coal tar, it was also recognised as a pyrolytic degradation product of cinchonamine, an alkaloid closely related to quinine, from which the name quinoline is derived

آلکالوئید ها:

از مهم ترین فرآورده ای حاصل از متابولیسم ثانویه در گیاهان بوده و دارای یک یا چند اتم نیتروژن (منبع ذخیره نیتروژن) و خاصیت قلیایی (بازی) می باشند و تاکنون بیش از 5000 نوع آلکالوئید شناسایی شده است.

آلکالوئید ها ممکن است در اندام های مختلف گیاهان از قبیل پوست (ریشه انار) ، کپسول (خشخاش) ، برگ (تاتوره) ، میوه (شاهدانه) ، دانه (بذر البنگ) یافت شوند.

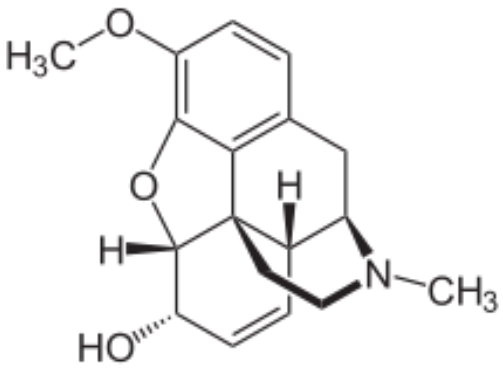
خواص و تاثیر عمده آلکالوئید ها بر روی سیستم عصبی و خاصیت مسکنی مانند آلکالوئید های مرفین در خشخاش می باشد . از سایر خواص آنها می توان به خاصیت ضد سرطانی آلکالوئید های وین کریستین و وین بلاستین در سورنجان ، ضد انقباض در تاتوره ، محرک آلکالوئید کافئین در قهوه و چای ، خلسه آور آلکالوئید مسکالین در کاکتوس ، ضد کرم و انگل در ریشه انار و... نام برد.

از خانواده های (تیره های) بدون آلکالوئید می توان به Lamiaceae ، Rosaceae، Coniferae و از خانواده های دارای آلکالوئید می توان به Solanacea ، Papaveraceae و Rubiaceae اشاره نمود.

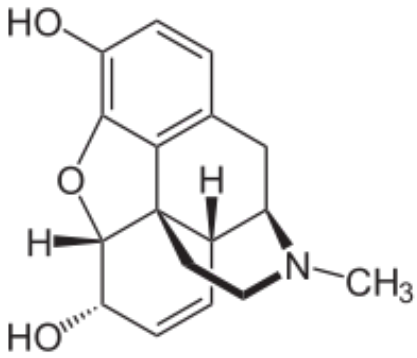
تذکر مهم:
از آنجا که آلکالوئید ها اکثرا سمی و مرگ آور می باشند استخراج و استفاده از گیاهان دارویی آلکالوئید دار تنها و تنها باید در کارخانه های مربوطه و زیر نظر متخصصان فن صورت گیرد.

نقش آلکالوئید ها در گیاهان:
منبع ذخیره نیتروژن
دافع برخی آفات و حشرات و علف خواران
تنظیم رشد گیاه

Some alkaloids



Codeine



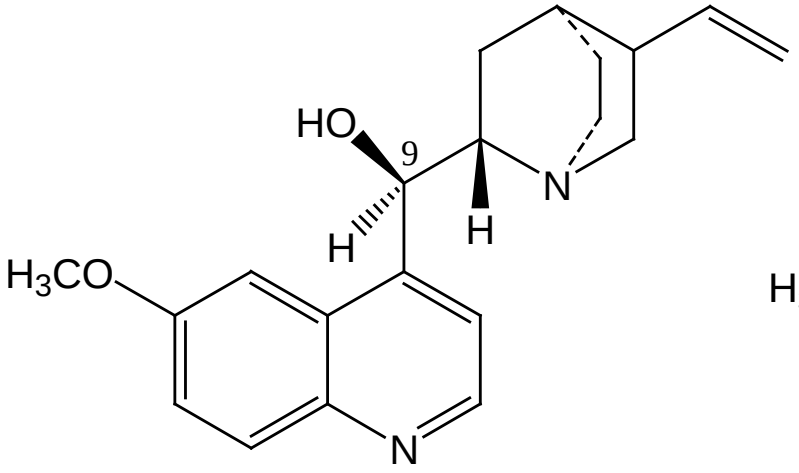
Morphine

Quinoline Alkaloids *Cinchona* Alkaloids

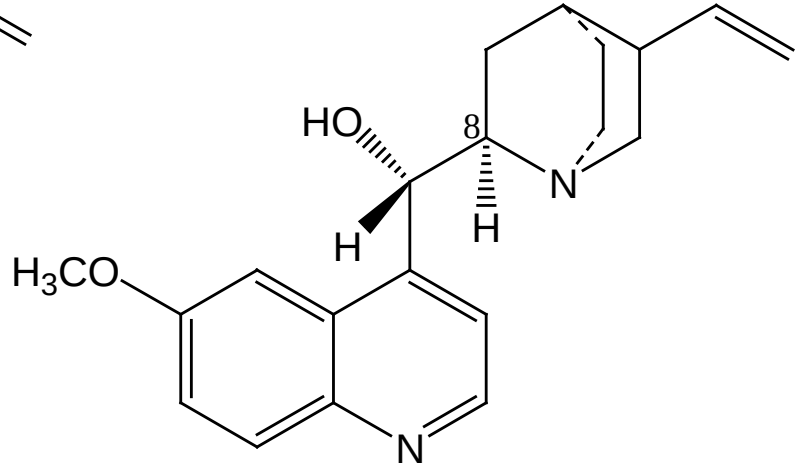
- **Cinchona bark contains many alkaloids, the majors are:**
  1- Quinine and Quinidine.
  2- Cinchonine and Cinchonidine.
- **Cinchona alkaloids are present as salts with Quinic and Cinchotannic acids.**

- **They are diacidic bases form two types of salts:**
  1- Neutral salts (Monoacidic) (less water soluble).
  2- Acidic salts (Diacidic) water soluble.

- Both Quinine and Quinidine, Cinchonine and Cinchonidine are diastereoisomers. Each pair differs in the stereochemistry at C-8 and C-9.

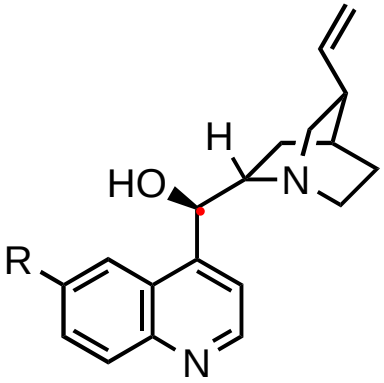


Quinine



Quinidine

Quinoline alkaloids

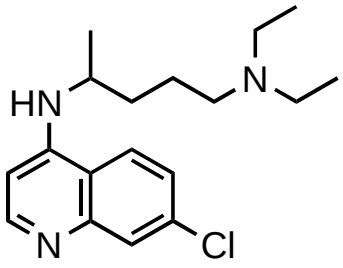


Cinchona pubescens (Kinatre) from South America

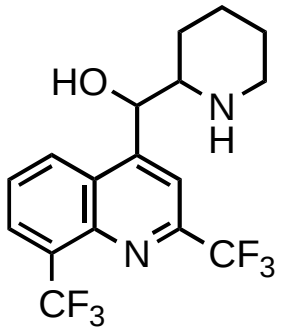
R=OMe: Quinine (Cinchonidine epimer at C-9)

R=H: Quinidine (Cinchonine epimer at C-9)

Quinidine: Antiarytmic
Quinine: Antimalaria



Chloroquine

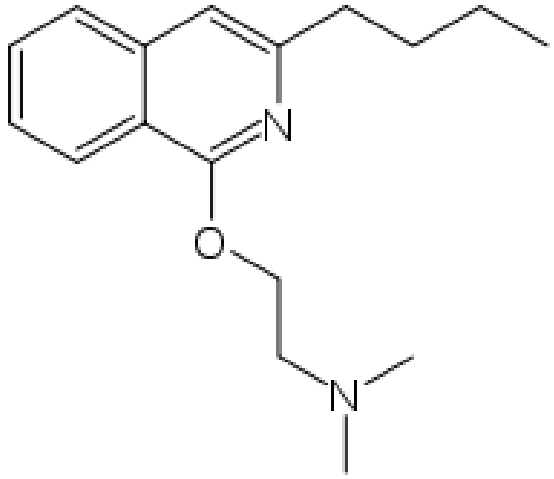


Mefloquine

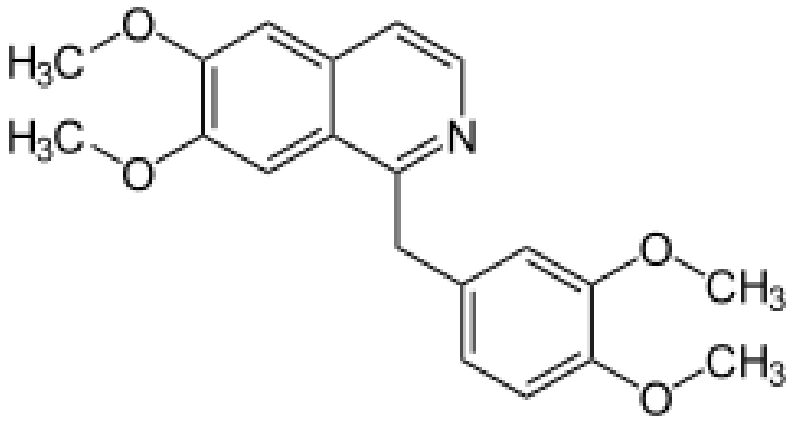
Dihydroquini(di)ne and deriv.
Chiral ligands
Asym. dihydroxylation (Sharpless)

Applications of Isoquinoline derivatives

anesthetics; dimethisoquin



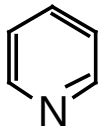
vasodilators, a well-known example, papaverine



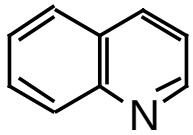
BENZO CONDENSED PYRIDINES: QUINOLINES AND ISOQUINOLINES

9.1 Reactions with Electrophilic Reagents

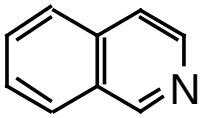
9.1.1 Protonation



pKa 5.2



pKa 4.9

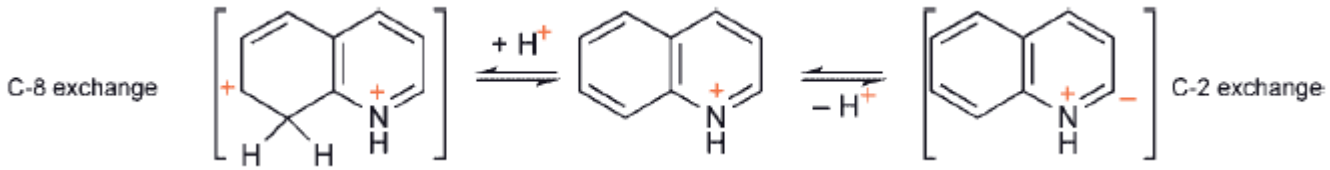


pKa 5.5

9.1.2 Substitution at Carbon

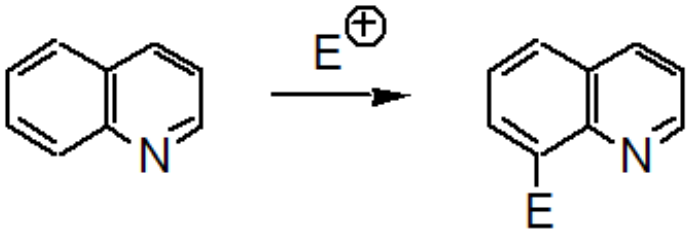
9.1.2.1 Proton Exchange

Benzene ring *C-protonation, and thence exchange, via N - protonated quinoline, requires strong sulfuric acid* and occurs fastest at C-8, then at C-5 and C-6; comparable exchange in isoquinoline takes place somewhat faster at C-5 than at C-8. At lower acid strengths each system undergoes exchange α to nitrogen, at C-2 for quinoline and C-1 for isoquinoline. These processes involve a zwitterion produced by deprotonation of the *N - protonated heterocycle.*

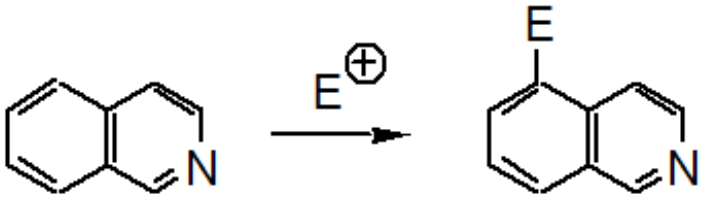


and C-1 for isoquinoline

Electrophilic Aromatic Substitution

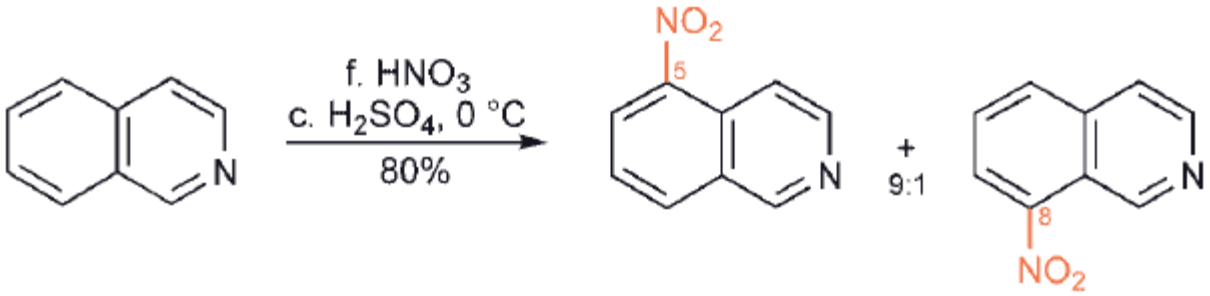


+ 5-isomer

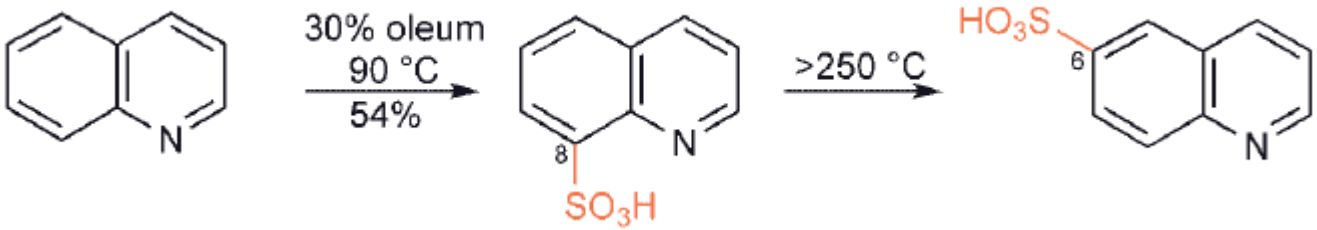


+ 8-isomer

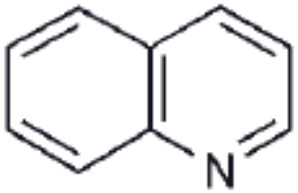
9.1.2.2 Nitration



9.1.2.3 Sulfonation



9.1.2.4 Halogenation

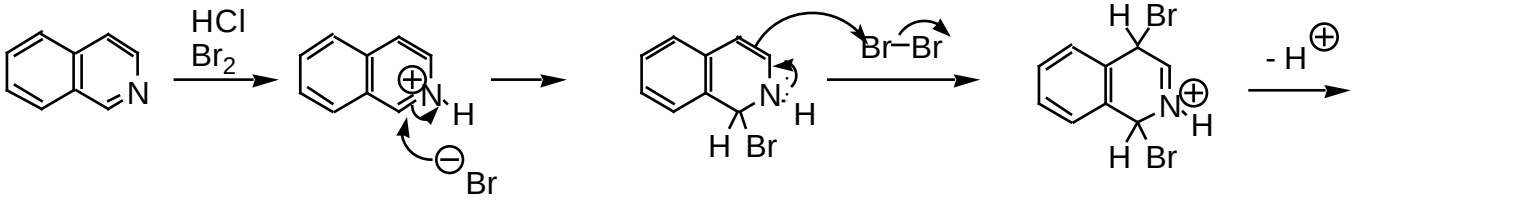


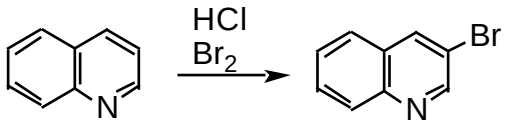
$$\xrightarrow{Br_2/H_2SO_4} \text{5-Br} + \text{8-Br}$$


N
Br2, AlCl3
75 °C
78%
Br
5
N

9.1.2.4 Halogenation

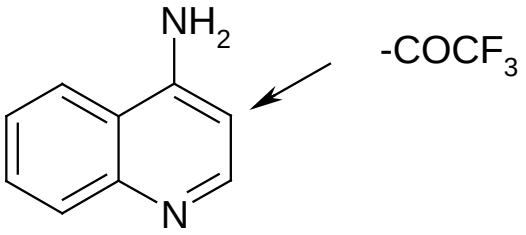
Halogenation in the Pyridine Ring of Hydrochloride salts:



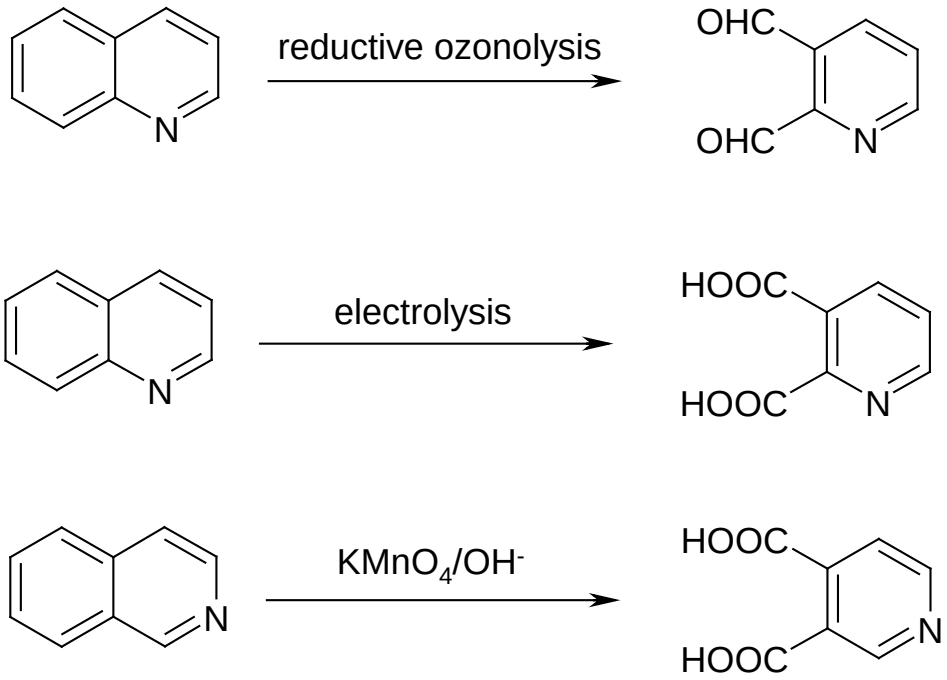


9.1.2.5 Acylation and Alkylation

There are no generally useful processes for the introduction of carbon substituents by electrophilic substitution of quinolines or isoquinolines, except for a few examples in which a ring has a strong electron - releasing substituent, for example 4-dimethylaminoquinoline undergoes smooth trifluoroacetylation at C-3.



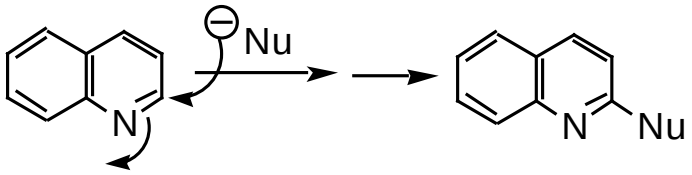
Oxidation


reductive ozonolysis
OHC
OHC
N
electrolysis
HOOC
HOOC
N
KMnO4/OH-
HOOC
HOOC
N

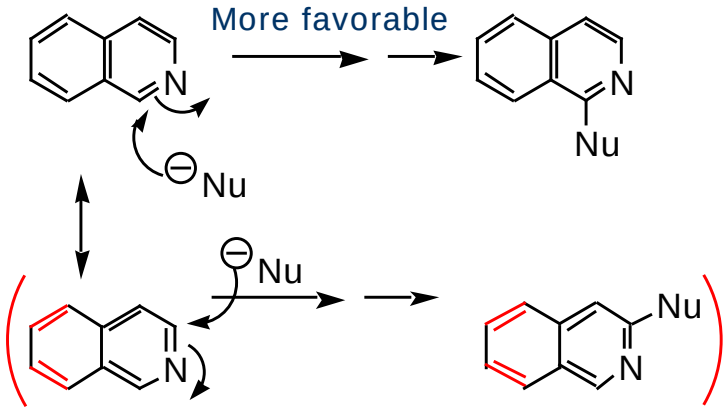
9.3 Reactions with Nucleophilic Reagents

9.3.1 Nucleophilic Substitution with ‘ Hydride ’ Transfer

Reactions of this type occur fastest at C-2 in quinoline and at C-1 in isoquinolines.

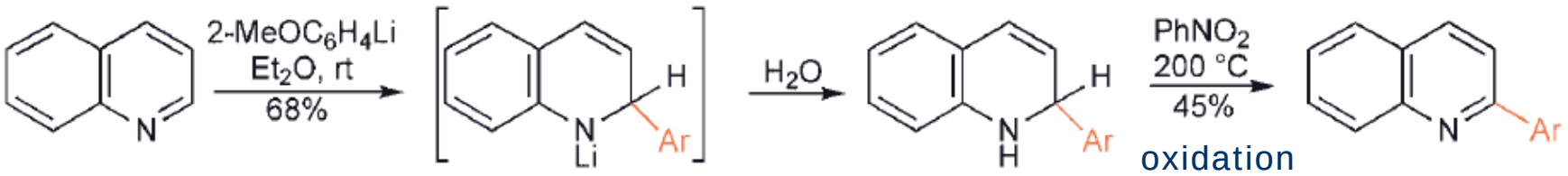


Nu-radicals (Minisci react.) attacks in the same pos.

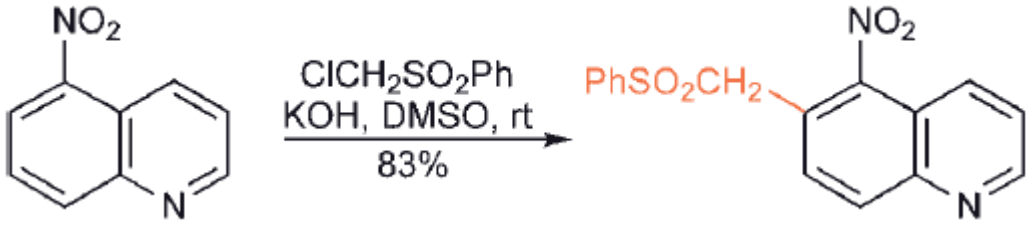


9.3.1.1 Alkylation and Arylation

The immediate products of addition of alkyl and aryl Grignard reagents and alkyl - and aryllithiums are dihydro- quinolines and - isoquinolines and can be characterised as such, but can be oxidised to afford the *C-substituted, re-aromatised heterocycles; illustrated below is a 2-arylation of quinoline.*



Vicarious nucleophilic substitution allows the introduction of substituents into nitroquinolines: cyanomethyl and phenyl-sulfonylmethyl groups, for example, can be introduced *ortho to the nitro group*, in 5-nitroquinolines at C-6 and in 6-nitro-quinolines at C-5.

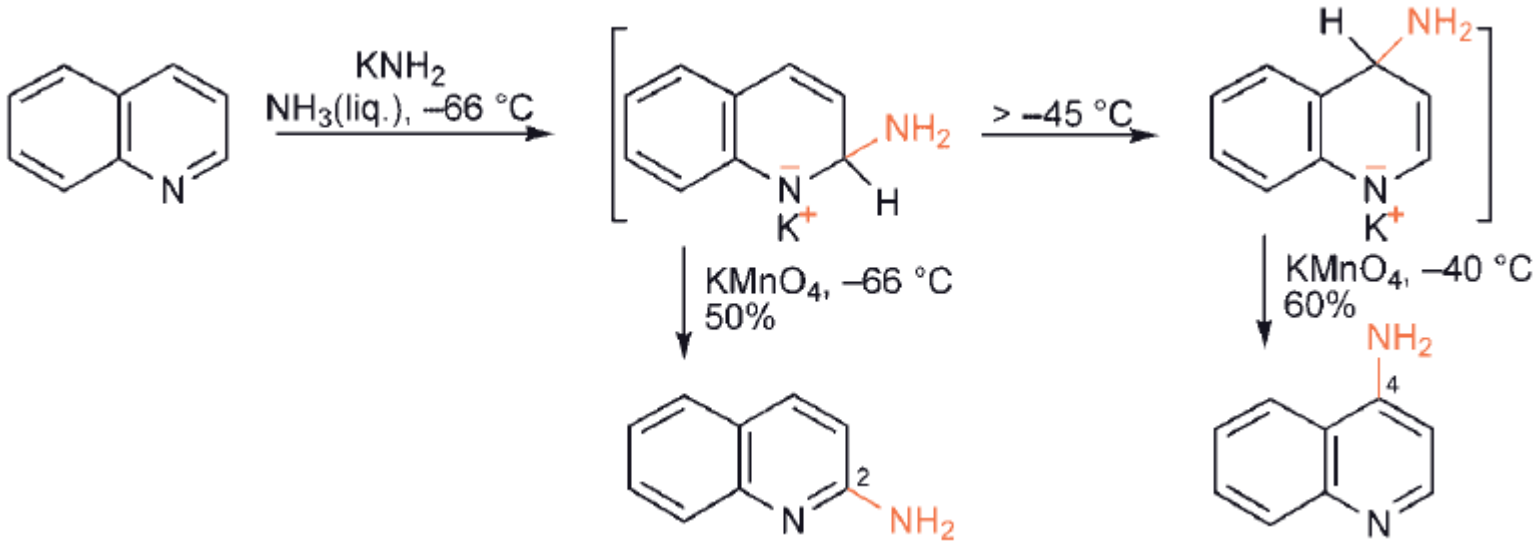


9.3.1.2 Amination and Nitration

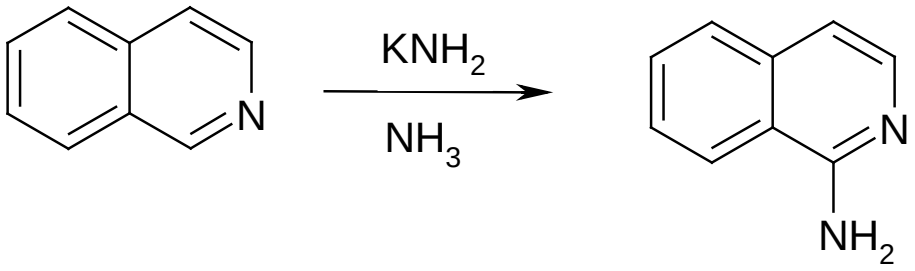
Sodium amide reacts rapidly and completely with quinoline and isoquinoline, even at − 45 ° C, to give dihydro - adducts with initial amide attack at C-2 (main) and C-4 (minor) in quinoline, and C-1 in isoquinoline.

The quinoline 2-adduct rearranges to the more stable 4-aminated adduct at higher temperatures.

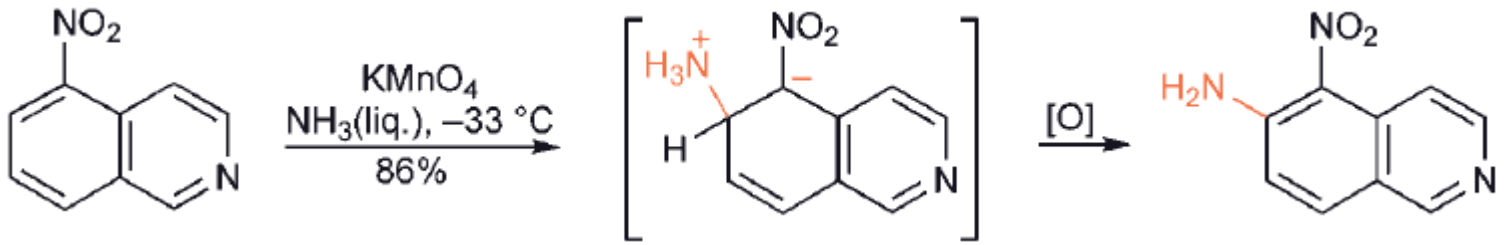
Oxidative trapping of the quinoline adducts provides 2- or 4-aminoquinoline;



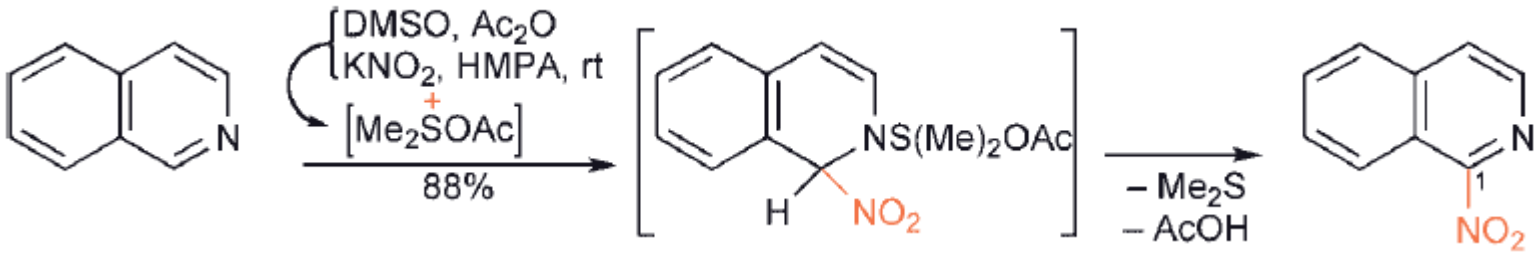
isoquinoline reacts with potassium amide in liquid ammonia at room temperature to give 1-aminoisoquinoline



Oxidative aminations are possible at other quinoline and isoquinoline positions, even on the benzene ring, providing a nitro group is present to promote the nucleophilic addition.

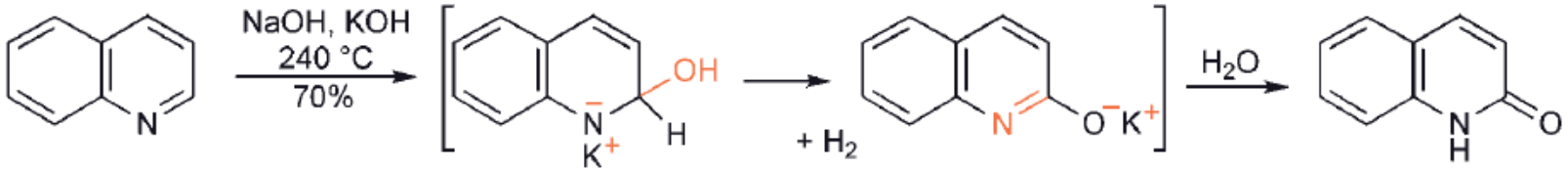


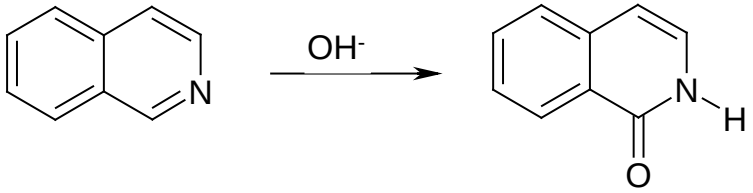
The introduction of a nitro group at C-1 in isoquinolines can be achieved using a mixture of potassium nitrite, dimethylsulfoxide and acetic anhydride. The key step is the nucleophilic addition of nitrite to the heterocycle previously quaternised by reaction at nitrogen with a complex of dimethylsulfoxide and the anhydride.



9.3.1.3 Hydroxylation

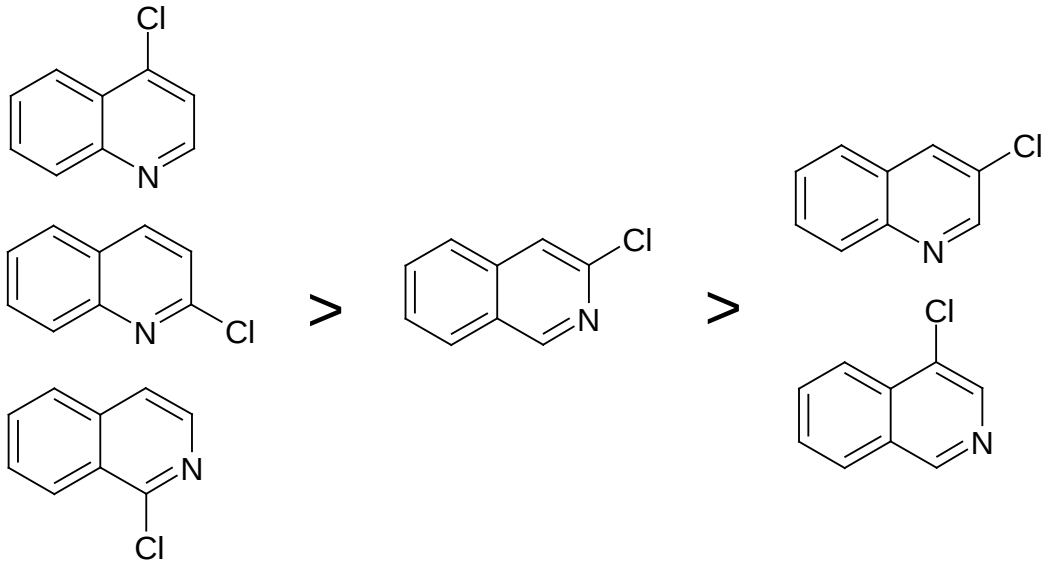
Both quinoline and isoquinoline can be directly hydroxylated with potassium hydroxide at high temperature with the evolution of hydrogen. 2-Quinolone (‘carbostyril’) and 1-isoquinolone (‘isocarbostyril’) are the isolated products.

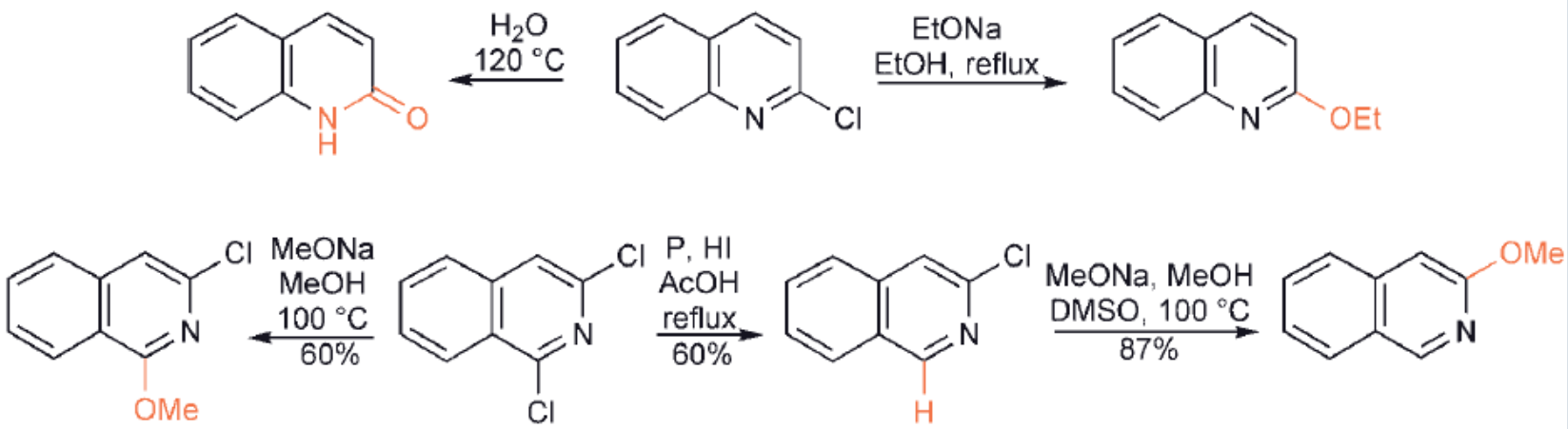




9.3.2 Nucleophilic Substitution with Displacement of Good Leaving Groups

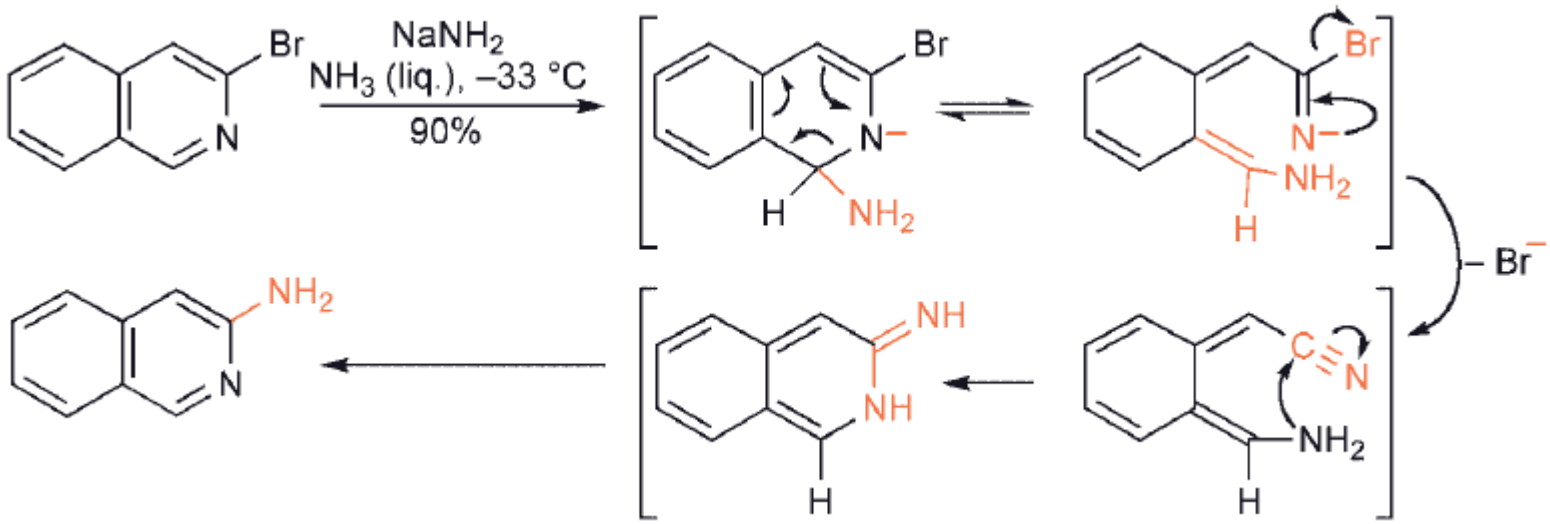
The main principle here is that halogen on the homocyclic rings of quinoline and isoquinoline, and at the quinoline-3- and the isoquinoline-4 positions, behaves as would a halobenzene. In contrast, 2- and 4-haloquinolines and 1-haloisoquinolines have the same susceptibility as α- and γ- halopyridines. 3-Halo-isoquinolines are intermediate in their reactivity to nucleophiles.



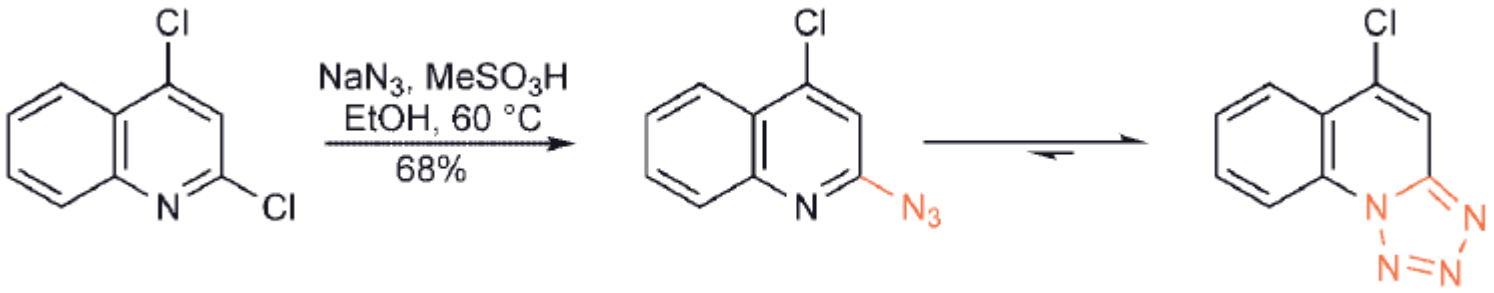

H2O
120 °C
EtONa
EtOH, reflux
MeONa
MeOH
100 °C
60%
P, HI
AcOH
reflux
60%
MeONa, MeOH
DMSO, 100 °C
87%

ANRORC (Add. Of Nu., Ring Opening and Ring Closure)

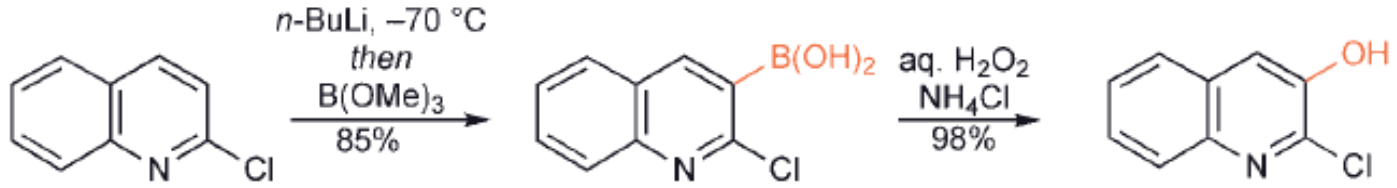
An apparent exception to the relative unreactivity of 3-halo - isoquinolines is provided by the reaction of 3-bromoisoquinoline with sodium amide. Here, a different mechanism, known by the acronym ANRORC (**Addition of Nucleophile, Ring Opening and Ring Closure)**, leads to the product, apparently of direct displacement, but in which a switching of the ring nitrogen to become the substituent nitrogen, has occurred.



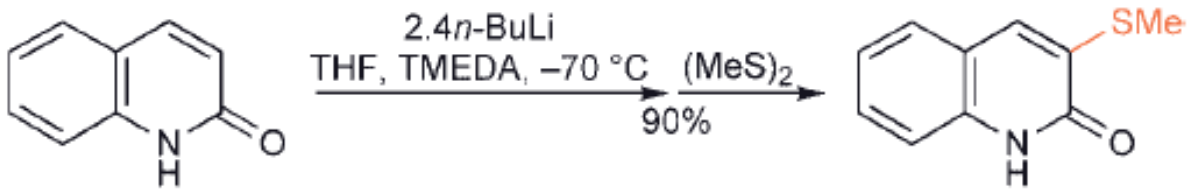
The reaction of 2,4-dichloroquinolines with an equivalent of sodium azide results in selective displacement at the 4-position, but, if an acid is added, the 2-position is preferred; the 2-azides exist as a ring/chain mixture, the tricyclic tetrazolo[1,5-*a]quinoline predominating.*



Direct lithiation, i.e. *C-deprotonation of quinolines* ***requires an adjacent substituent****, such as chlorine,* fluorine or alkoxy.

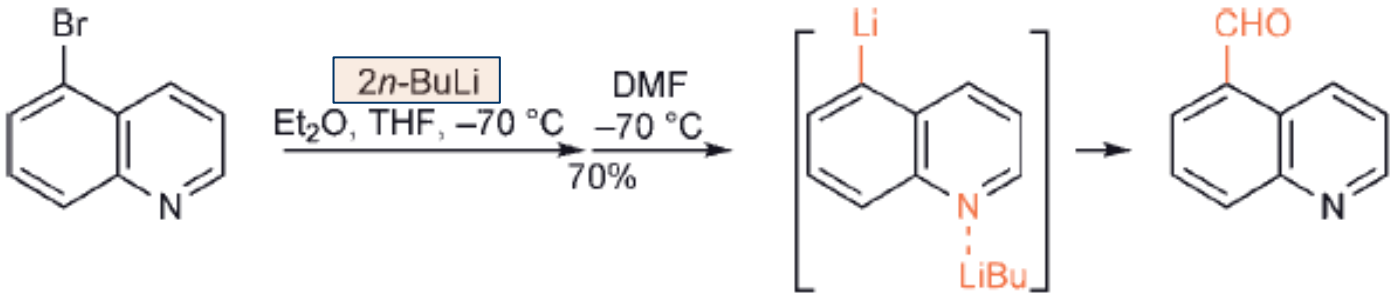


2-Lithiation of 1-substituted 4-quinolones and 3-lithiation of 2-quinolone provides derivatives with the usual nucleophilic propensity, as illustrated below.



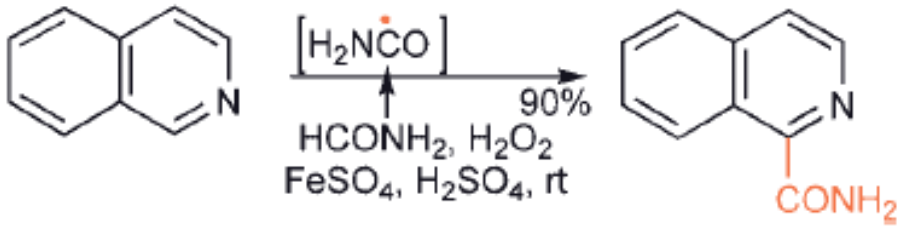
9.4.2 Metal – Halogen Exchange

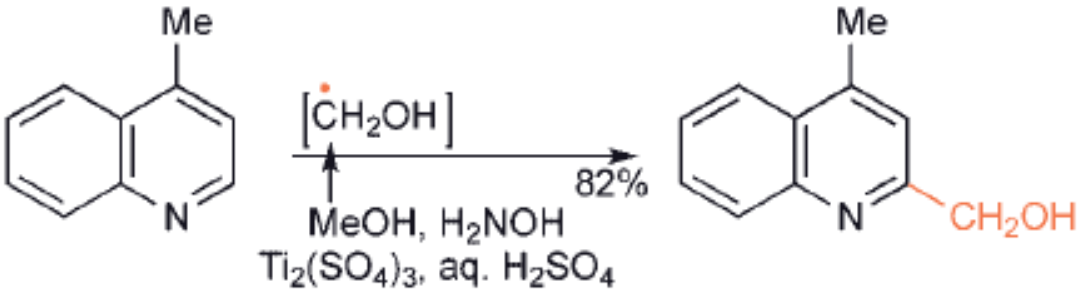
The preparation of lithio-quinolines and -isoquinolines *via metal–halogen exchange is complicated by* competing nucleophilic addition, however the use of low temperatures does allow metal – halogen exchange at both pyridine and benzene ring positions in quinolines, and the isoquinoline.



9.5 Reactions with Radicals

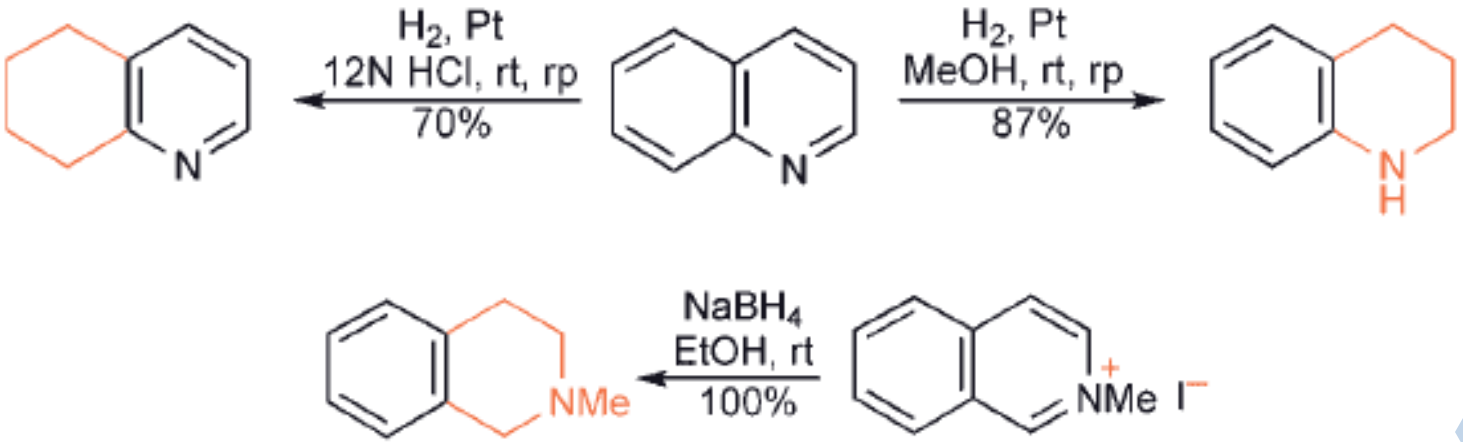
Regioselective substitutions can be achieved α to the nitrogen, with nucleophilic radicals, in acid solution– the Minisci reaction.





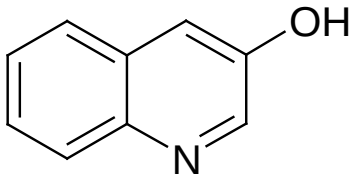
9.6 Reactions with Reducing Agents

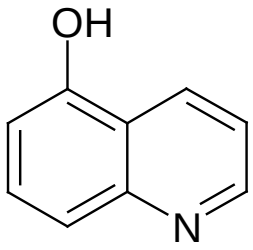
Selective reduction of either the pyridine or the benzene rings in quinoline and isoquinoline can be achieved:
the heterocyclic ring is reduced to the tetrahydro level by sodium cyanoborohydride in acid solution, by sodium boro-hydride in the presence of nickel(II) chloride, by zinc borohydride or, traditionally, by room temperature and room pressure catalytic hydrogenation in methanol. In strong acid solution it is the benzene ring which is selectively saturated; longer reaction times can then lead to decahydro derivatives.



Oxy - Quinolines and Oxy - Isoquinolines

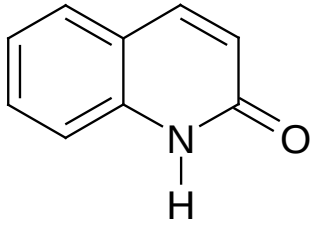
Quinolinols and isoquinolinols in which the oxygen is at any position other than C-2 or C-4 for quinolines and C-1 or C-3 for isoquinolines are true phenols i.e. have an hydroxyl group, though they exist in equilibrium with variable concentrations of zwitterionic structures, with the nitrogen protonated and the oxygen deprotonated. They show the typical reactivity of naphthols.

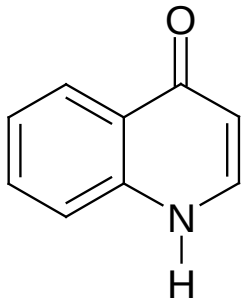




etc.

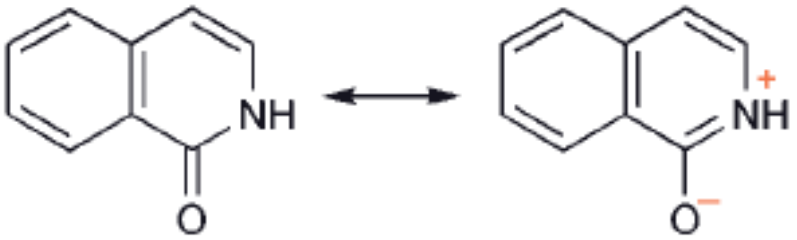
but:





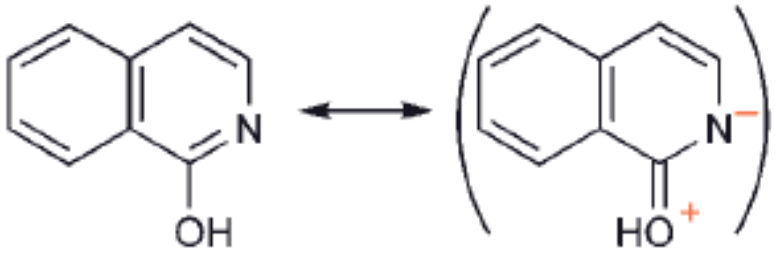
Oxy - Quinolines and Oxy - Isoquinolines

For *2*-Quinolone , *4-quinolone and 1-isoquinolone,* the hydroxyl tautomers lack a favourable polarised resonance contribution, as illustrated below for 1 - isoquinolone.



1-isoquinolone
[2*H*-isoquinolin-1-one]

favourable

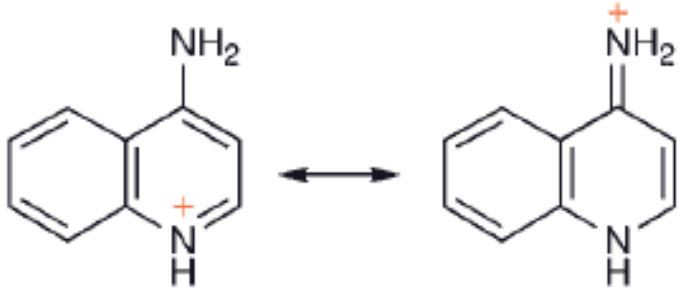


isoquinolin-1-ol

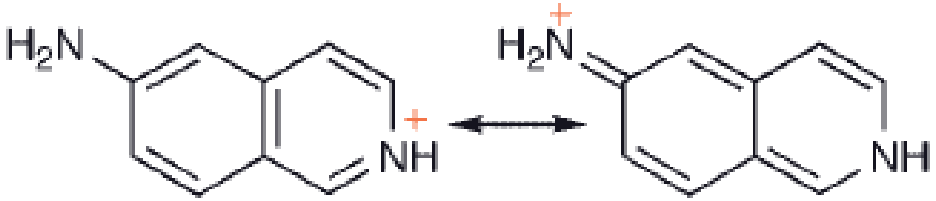
Non-favourable

Amino- Quinolines and Amino- Isoquinolines

Amino- quinolines and -isoquinolines exist as amino tautomers and all protonate on ring nitrogen. Only 4-aminoquinoline (pK_aH *9.2) and* the 6-isomer (pK_aH *7.2, the most basic amino-isoquinoline)*, shows appreciably enhanced basicity.



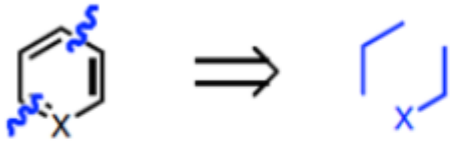
4-aminoquinolinium protocation

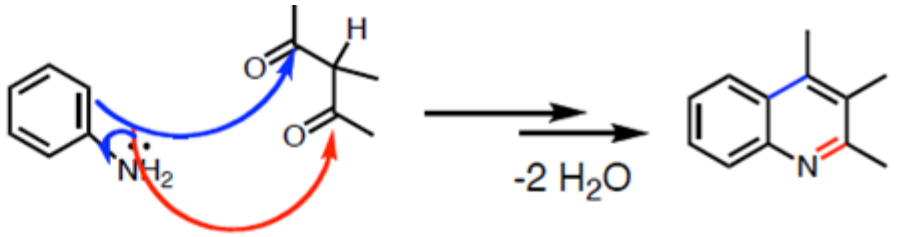


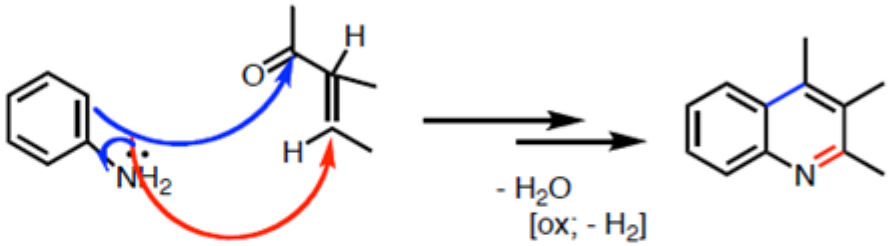
6-aminoisoquinolinium protocation

Synthesis - Quinolines

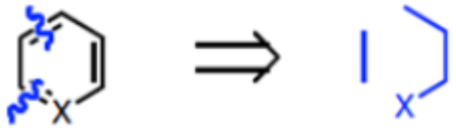
Chapt. 3
Strategy b, 6-membered rings

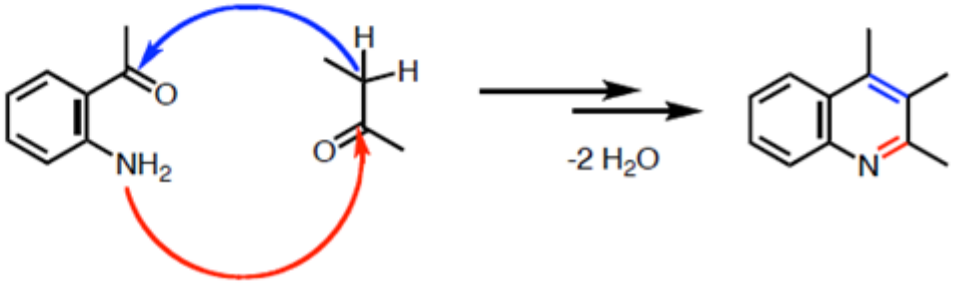






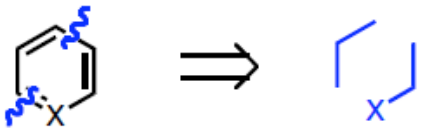
"New" strategy

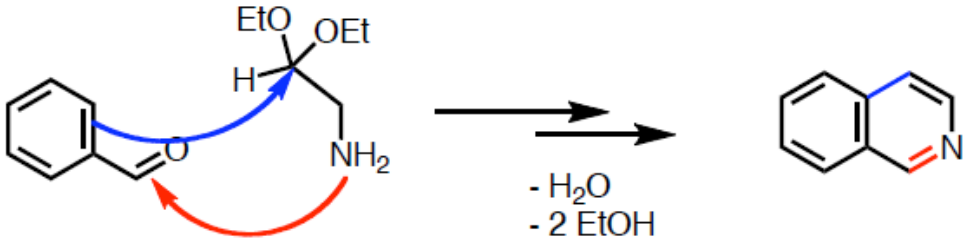




Synthesis - Isoquinolines

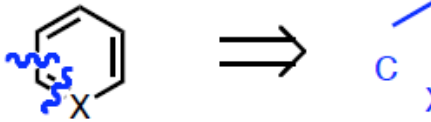
Chapt. 3
Strategy b, 6-membered rings

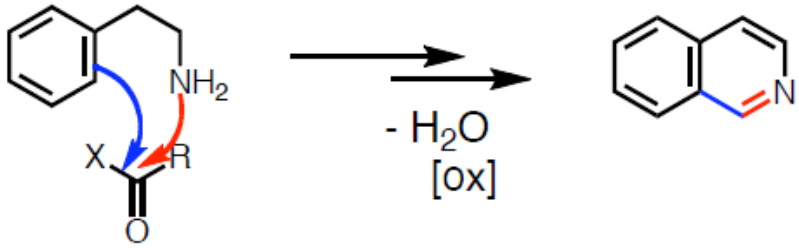




"Blue bonds" formed by FC type react.

"New" strategy

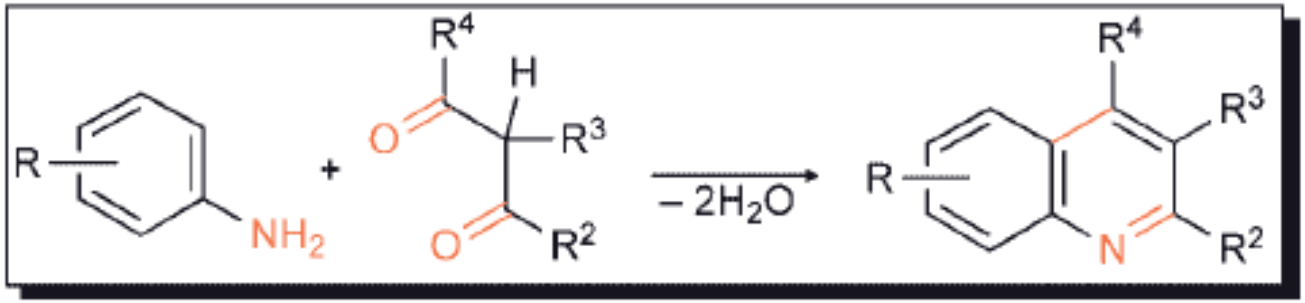




X: -Cl, H

Quinolines from Aryl Amines and 1,3-Dicarbonyl Compounds

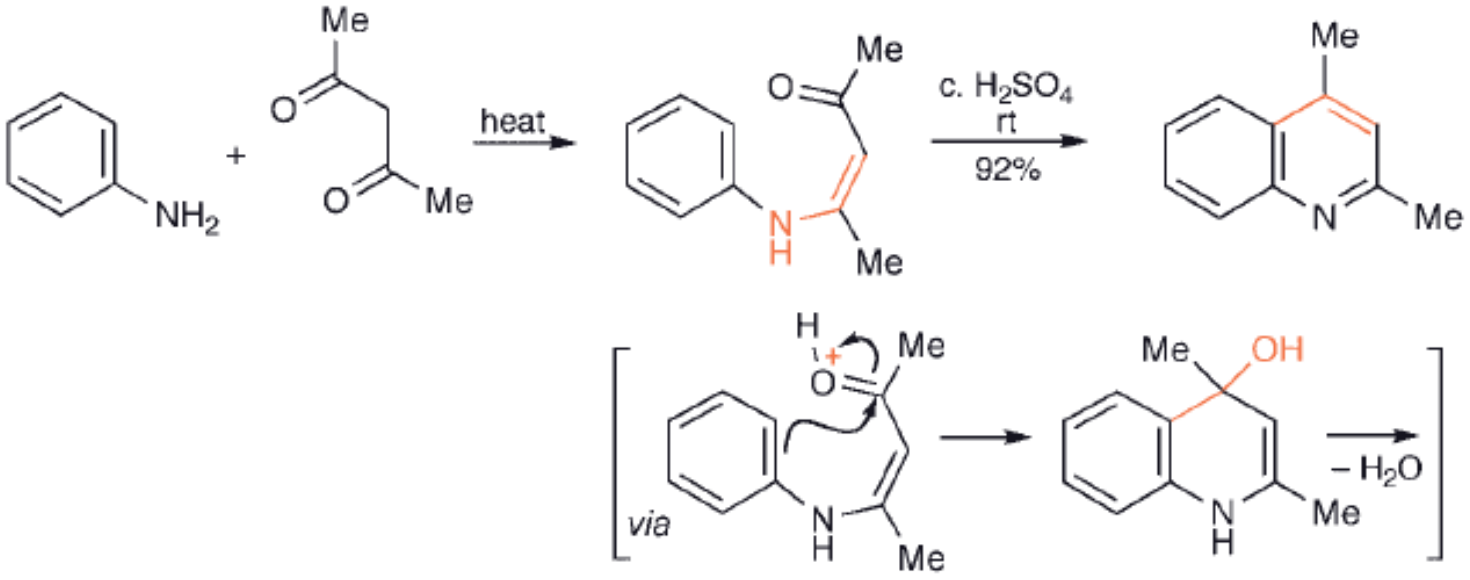
Anilines react with 1,3-dicarbonyl compounds to give intermediates which can be cyclised with acid.



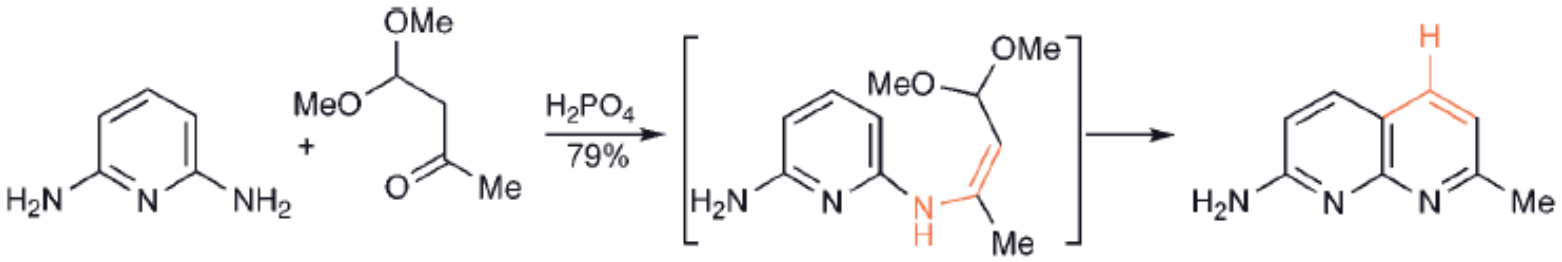
Quinolines from Aryl-Amines and 1,3-Dicarbonyl Compounds

The Combes Synthesis

Condensation of a 1,3-dicarbonyl compound with an aryl-amine gives a high yield of a β-aminoenone, which can then be cyclised with concentrated acid. Mechanistically, the cyclisation step is an electrophilic substitution by the *O-protonated aminoenone, followed by loss of water to give the aromatic* quinoline.

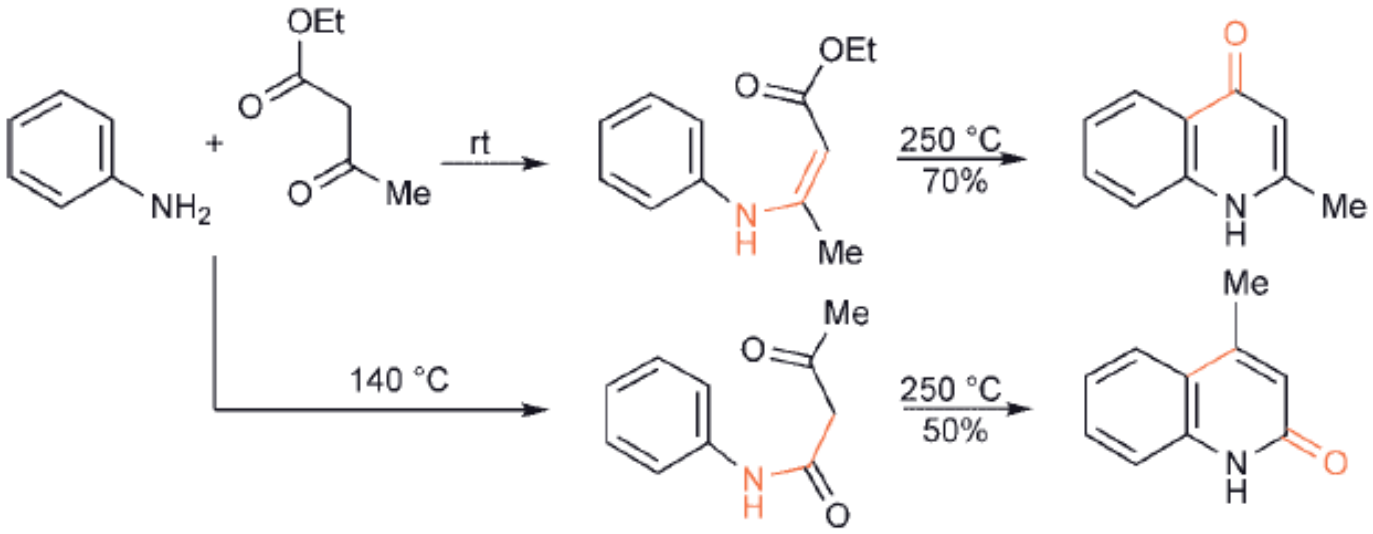


In order to access 4-unsubstituted quinolines, a 1,3- ketoaldehyde, in protected form, guarantees the required regioselectivity; the example below produces a 1,8-naphthyridine (pyrido[2,3-*b*]*pyridine).*

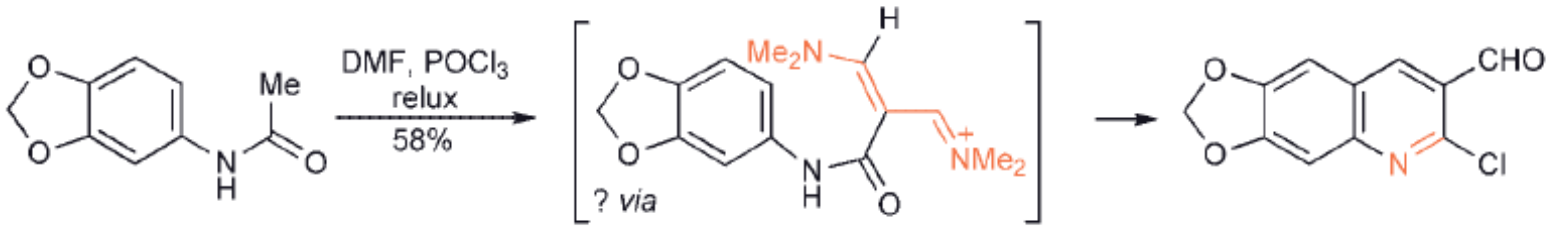


Conrad–Limpach–Knorr Reaction

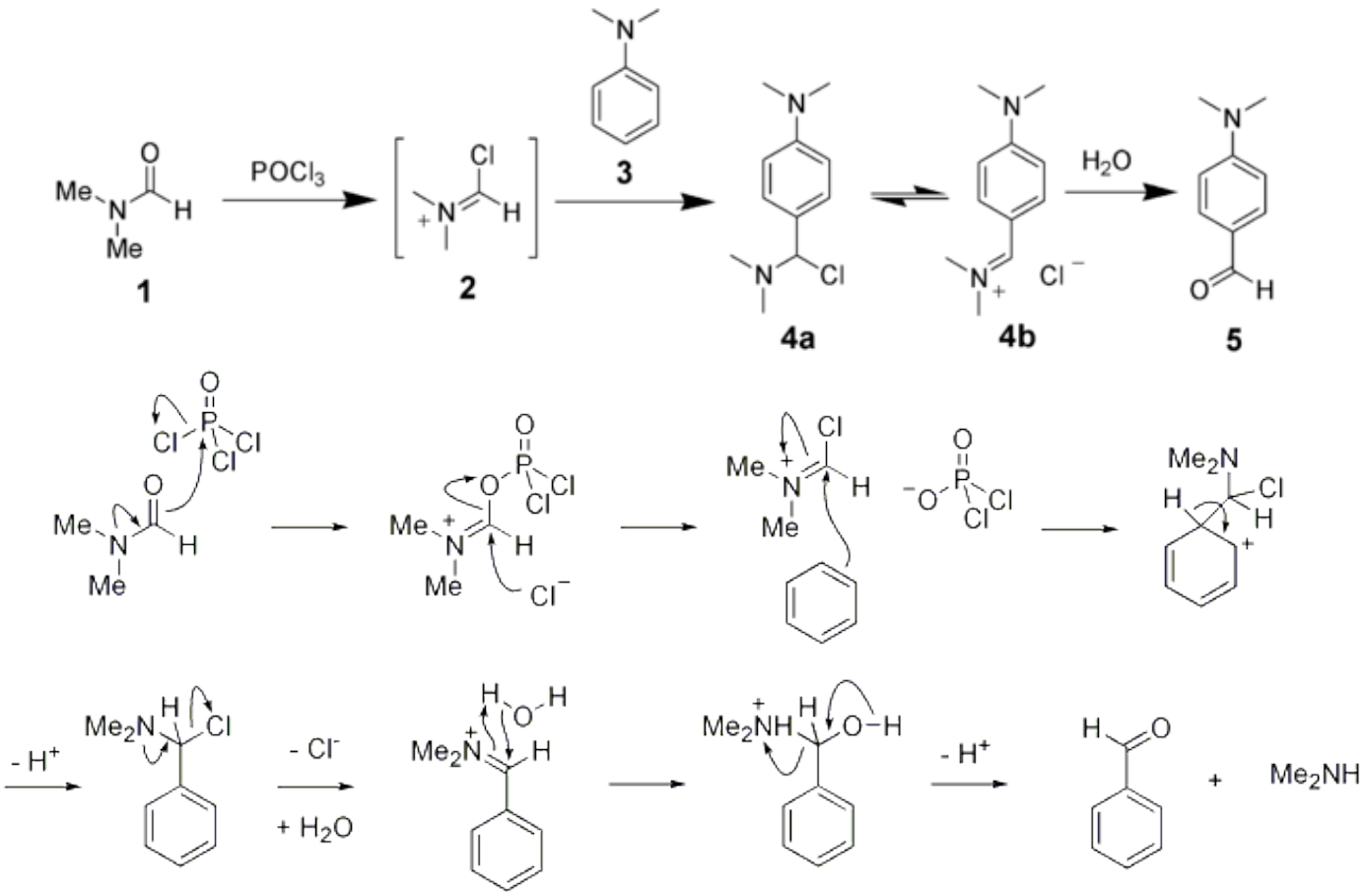
If the 1,3-dicarbonyl component is at the 1,3-keto acid oxidation level, then the product is a quinolone. Anilines and β-keto esters react at lower temperatures to give the kinetic product, a β-aminoacrylate, cyclisation of which gives a 4-quinolone. At higher temperatures, β-keto acid anilides are formed and cyclisation of these affords 2-quinolones.



Usefully functionalised quinolines are easily accessible from anilines: the *N-acetyl derivative is simply* reacted with the Vilsmeier reagent and a 2-chloro-3-formylquinoline results. One may speculate that a 3-formylanilide, or an equivalent (shown), is involved, placing this useful reaction into the Combes category.

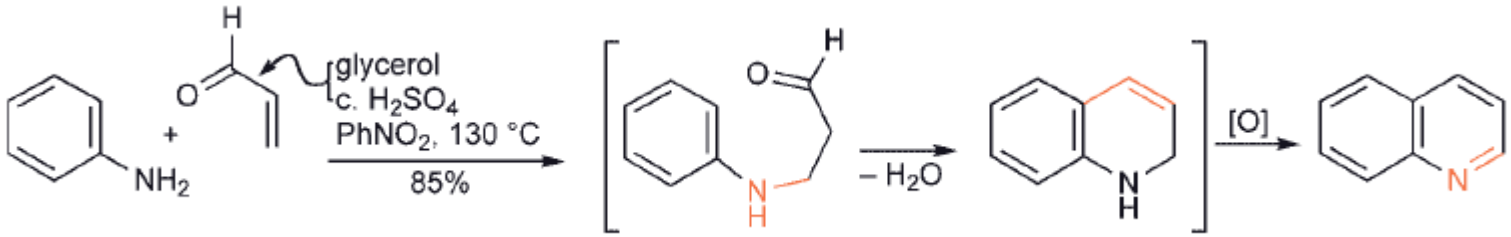


The Vilsmeier–Haack reaction



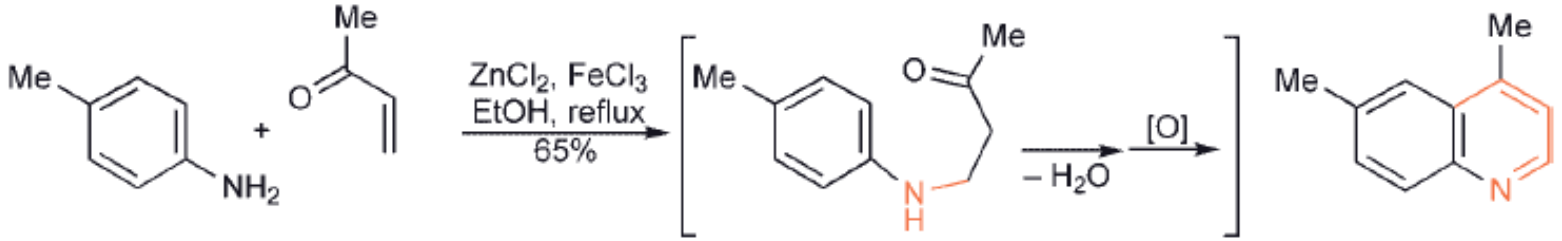
The Skraup Synthesis

In this extraordinary reaction, quinoline is produced when aniline, concentrated sulfuric acid, glycerol and a mild oxidising agent are heated together.



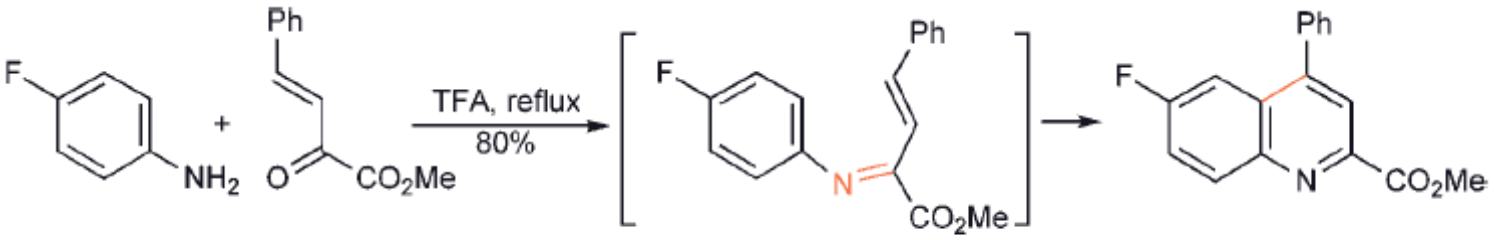
Doebner–Miller Synthesis

The use of an enone confirms the mechanism, showing that interaction of the aniline amino group with the carbonyl group is *not the first step, and this variation is known as the Doebner – Miller synthesis.*



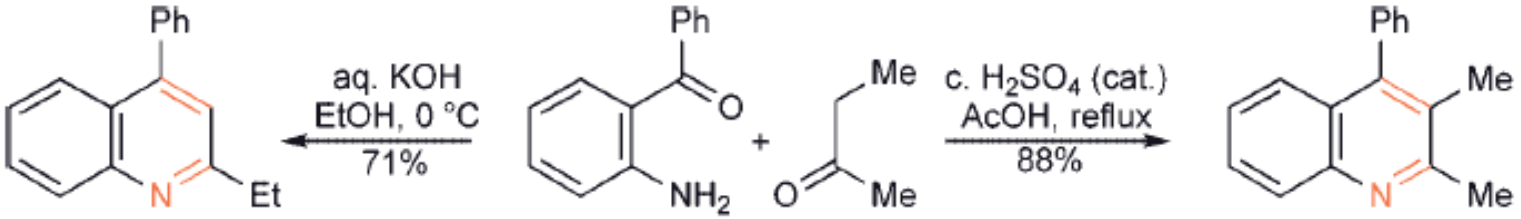
Improvements to the regime for Doebner–Miller ring closures include the use of a two - phase organic/aqueous acid system to minimize alkene polymerization and the use of indium(III) chloride on silica with microwave irradiation.

It is significant that the accepted and proved regiochemistry for these cyclisations is *reversed when the reaction is carried out in trifluoroacetic acid, imine formation being the first step, at* least for unsaturated 2-keto esters.

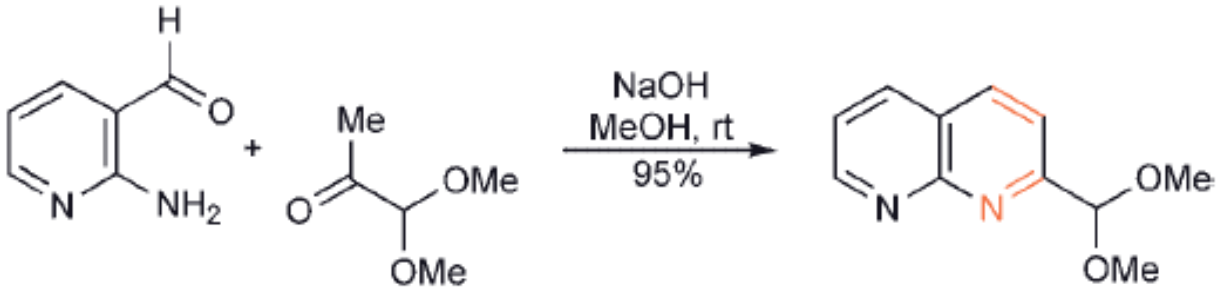


The Friedländer Synthesis

This route has been used extensively for the synthesis of substituted quinolines. In the original sequence, an *ortho-acyl-arylamine is condensed with a ketone or aldehyde (which must contain an* α*-methylene* group) by base or acid catalysis to yield the quinoline. The orientation of condensation depends on the regioselectivity of enolate or enol formation.

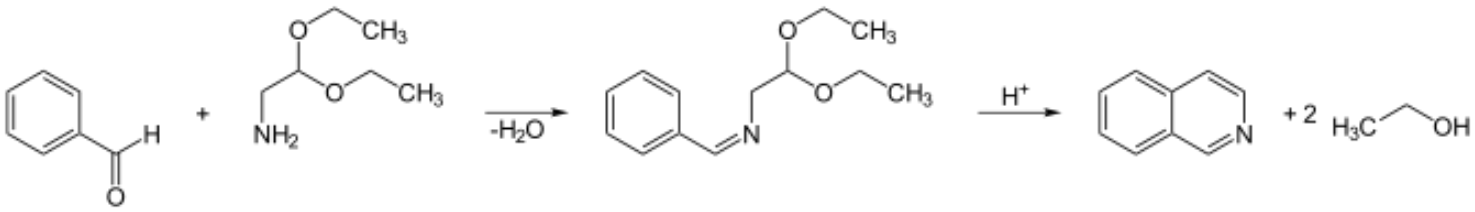


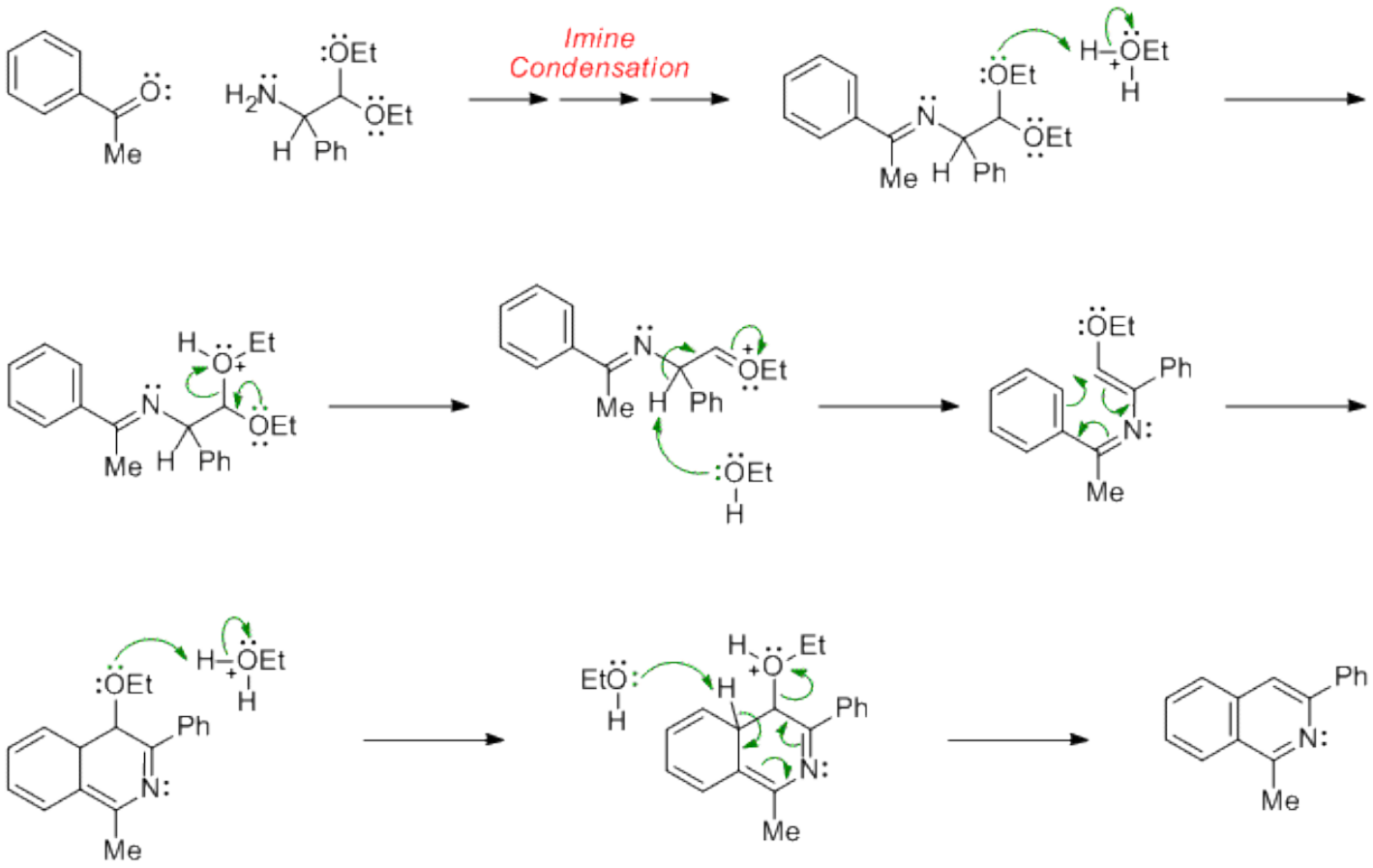
Naphthyridines can also be obtained utilising the Friedländer strategy:



Isoquinoline Synthesis, The Pomeranz – Fritsch Synthesis

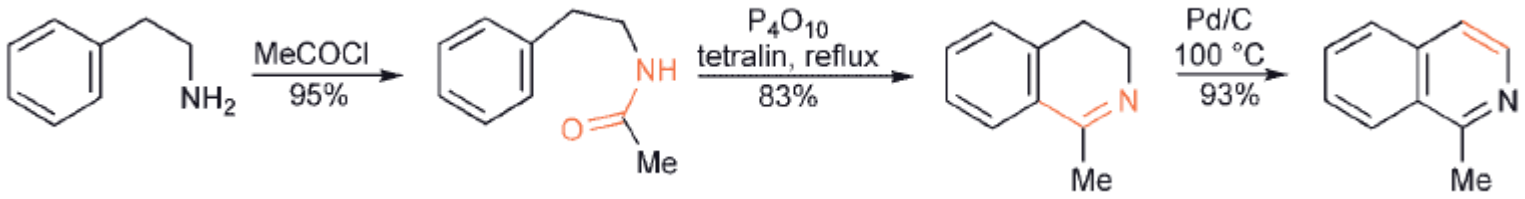
This reaction uses a benzaldehyde and aminoacetoaldehyde diethyl acetal, which in an acid medium react to form isoquinoline. Alternatively, benzylamine and a glyoxal acetal can be used, to produce the same result.




Imine
Condensation

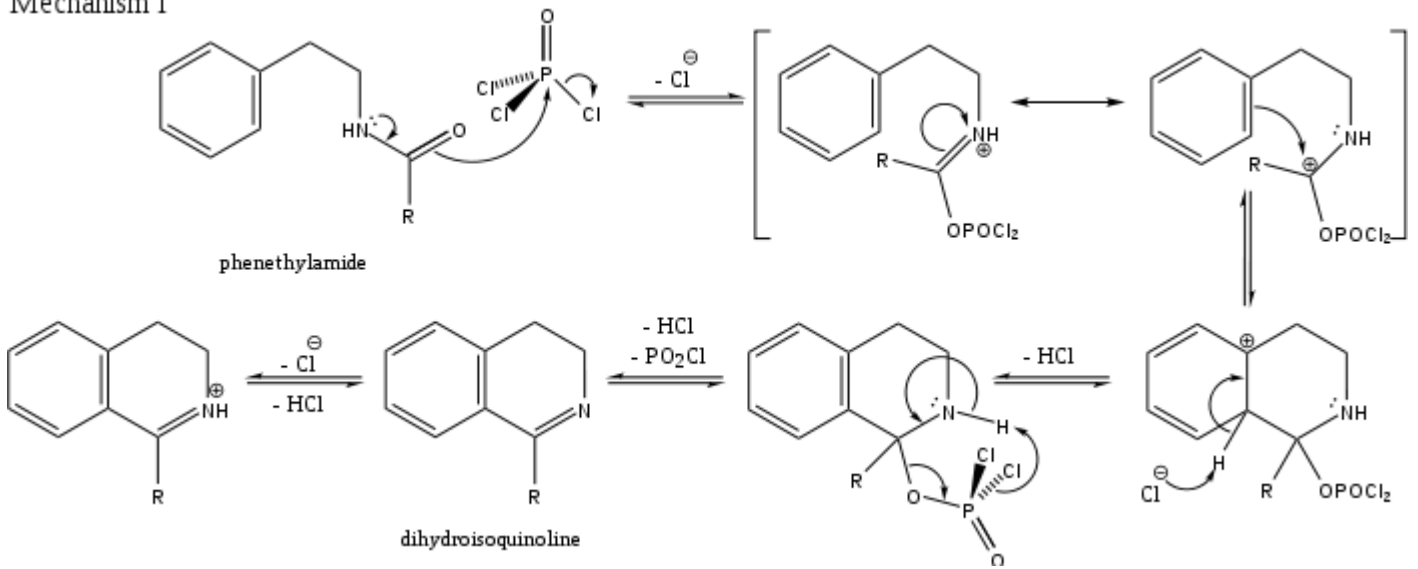
Bischler–Napieralski reaction

In the classical process, a 2-aryl-ethanamine reacts with a carboxylic acid chloride or anhydride to form an amide, which can be cyclised, with loss of water, to a 3,4-dihydro-isoquinoline, then readily dehydrogenated to the isoquinoline using, for example, palladium, sulfur or diphenyl disulfide. Common cyclisation agents are P2O5, often with phosphoryl chloride, and phosphorus pentachloride. The electrophilic intermediate is very probably an imino chloride, or imino phosphate; the former have been isolated and treated with Lewis acids when they are converted into isonitrilium salts, which cyclise efficiently to 3,4–dihydroisoquinolines.

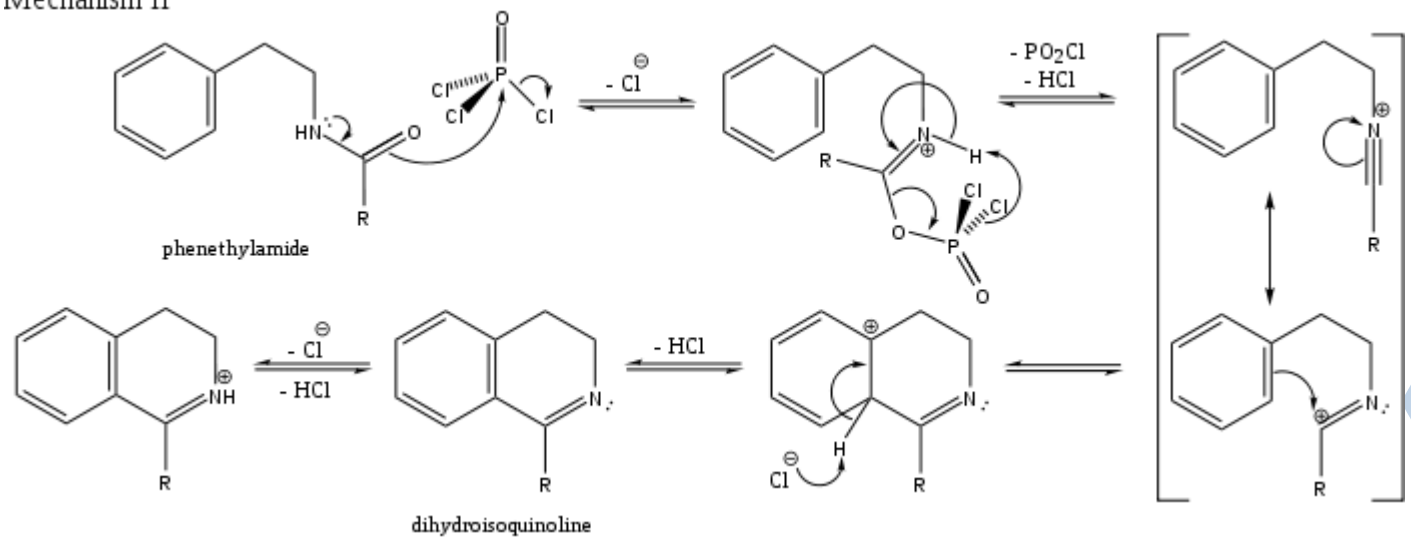


Bischler–Napieralski reaction

Mechanism I

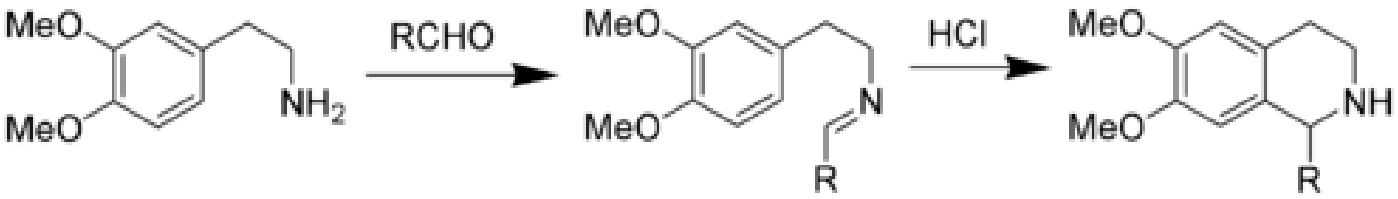


Mechanism II



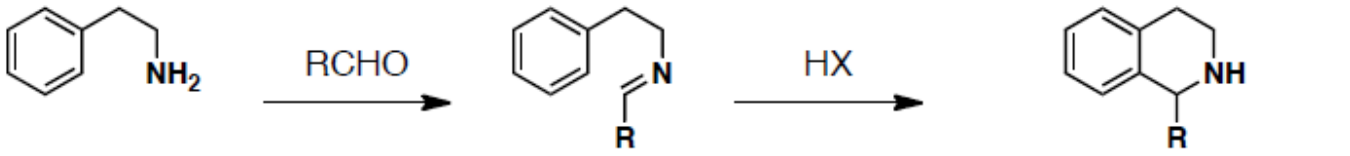
The Pictet-Spengler Reaction!

β-arylethylamine undergoes ring closure after condensation with an aldehyde or ketone. Usually an acidic catalyst is employed and the reaction mixture heated, but some reactive compounds give good yields even at physiologic conditions.

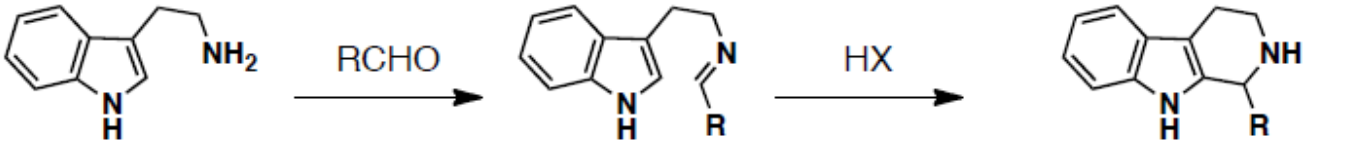


Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* ***1911, 44, 2030!2036.***

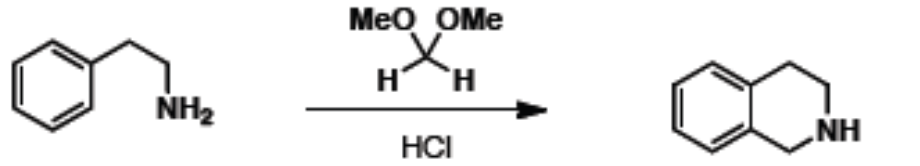
The Pictet–Spengler reaction can be considered as a special case of the Mannich reaction.



Tetrahydroisoquinoline



Tetrahydro-β-carboline



phenethylamine

tetrahydroisoquinoline

The **Mannich reaction** is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group with formaldehyde and ammonia or any primary or secondary amine. The final product is a β-amino-carbonyl compound also known as a Mannich base.