Chapter 10: Chemical and process development

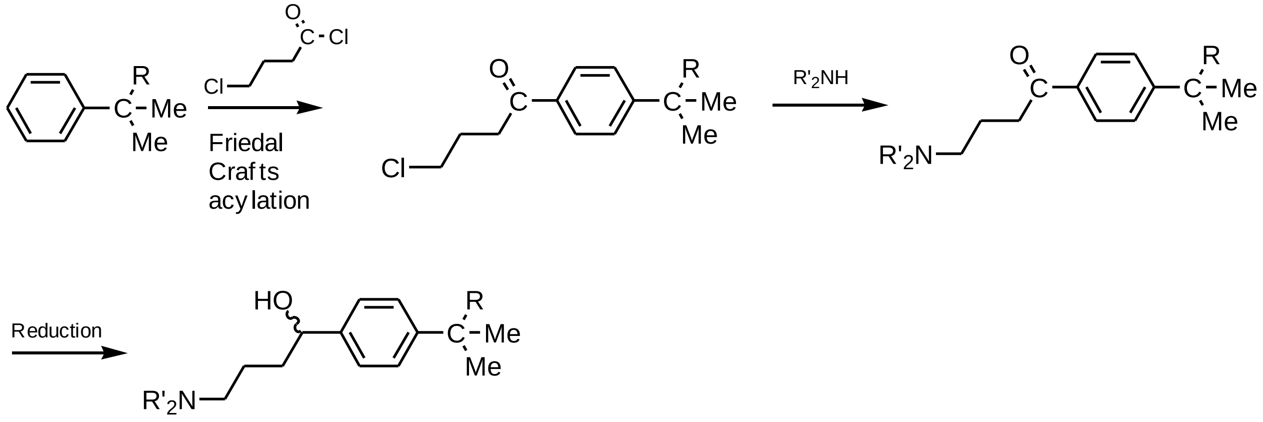
Question 10.1
Usually, a 'balancing act' of priorities is required during chemical development. Explain what this means.

Answer
In chemical development, the aim is to design a large scale synthesis which is cheap and fast, and which produces the final compound in high yield and high purity. However, it may not be possible to achieve all of these priorities. For example, high yield does not necessarily imply high purity, and a compromise between these two priorities may be necessary

Question 10.2
Discuss whether chemical development is simply a scale up exercise.

Answer
Scale up is certainly part of the chemical development process, but it is only part ot the process. Certain reactions may not be suitable for scale up due to the cost or toxicity of the chemical present. This would require altering the conditions of particular reactions or changing the synthetic route altogether

Question 10.3
The following synthetic route was used for the initial synthesis of fexofenadine (R=CO_2H) - an analogue of terfenadine (R=CH_3). The synthesis was suitable for the large-scale synthesis of terfenadine, but not for fexofenadine. Suggest why not. (Hint: consider the electronic effects of R)

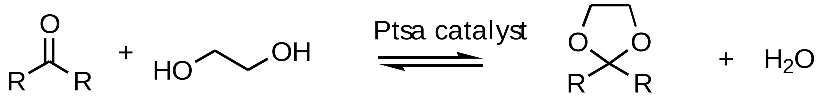


Answer
There is the problem with the first step of the reaction sequence - an electrophilic substitution of an aromatic ring. The carboxylic acid group in fexofenadine is electron withdrawing, whereas the methyl group in terfenadine is electron donating.
In the latter case, the Friedal Crafts acylation gives only the *para* product. Alkyl groups are electron donating and direct *ortho/para*. However, the alkyl group in terfenadine is branched and bulky, so it is unlikely that any *ortho* substitution will take place.

Turning to fexofenadine, the presence of the electron withdrawing carboxylic acid weakens the directing ability of the alkyl side chain. Consequently, both the *meta* and *para* products are obtained. these products have to be separated by chromatography which is inconvenient on large scale, especially at such an early stage of the synthesis.

Question 10.4

The following reaction was carried out with heating under reflux at 110^o C. However, the yield was higher when the condenser was set for distillation. Explain.

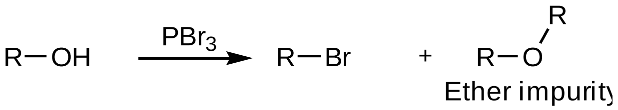


Answer
Water is produced in this reaction. If the condenser is set to reflux, the water remains in the reaction solution and the reaction proceeds to equilibrium.
If the condenser is set to distillation, water will be removed from the reaction solution. This removes one of the products of an equilibrium reaction and will pull the reaction through to completion.

Question 10.5
What considerations do you think have to be taken into account when choosing a solvent for scale up? Would you consider diethyl ether or benzene as a suitable solvent?

Answer
There are many considerations to be taken into account such as cost, commercial availability, purity, toxicity, volatility, flammability, flash point, ignition temperature, vapour density, solubility of the reagents and products in the chosen solvent, compatability of the solvent with the reaction attempted.
Diethyl ether should never be considered as a solvent for scale up. It is highly volatile and is flammable over a wide solvent/air range. It is heavier than air and can 'creep' along laboratory floors or benches. It can also be easily ignited by a spark or hot steam pipes.
Benzene should never be considered either since it is carcinogenic. Indeed, it is no longer used in small-scale preparations.

Question 10.6
Phosphorus tribromide was added to an alcohol to give an alkyl bromide, but the product was contaminated with an ether impurity. Explain how this impurity might arise and how the reaction conditions could be altered to avoid the problem.



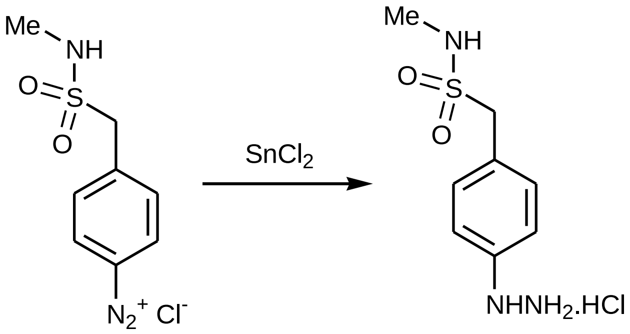
Answer

By adding phosphorus tribromide to the alcohol, the alkyl bromide will initially be formed in the presence of unreacted alcohol. As a result, the alcohol can react with the alkyl bromide to form the ether.

This can be avoided by adding the alcohol to the PBr_3 instead.

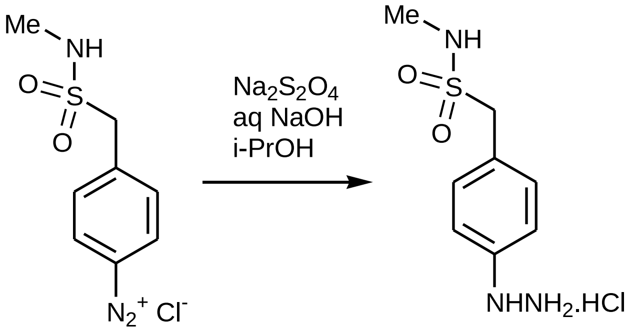
Question 10.7

Stannous chloride ($SnCl_2$) was used as a reducing agent in one of the early stages of a synthesis leading to sumatriptan. However, this was considered inappropriate for a large scale synthesis. Explain why and suggest an alternative reagent.



Answer

There are environmental concerns surrounding the use of stannous chloride ($SnCl_2$). It is toxic to aquatic organisms and could linger in soils and sediments. Sodium dithionite ($Na_2S_2O_4$) has fewer environmental problems and has an added advantage of being cheaper.

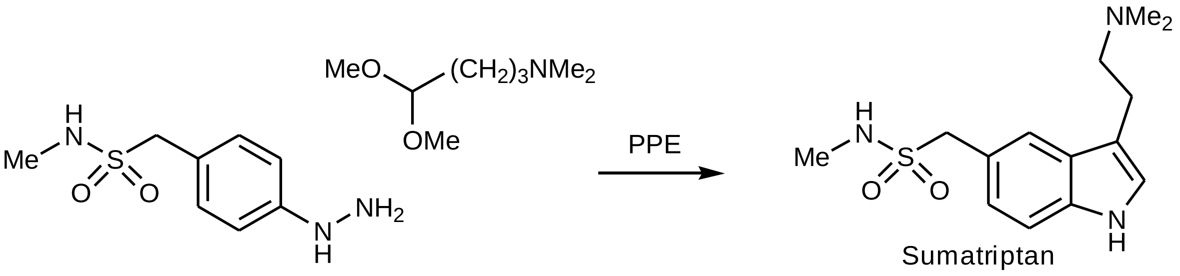


Question 10.8

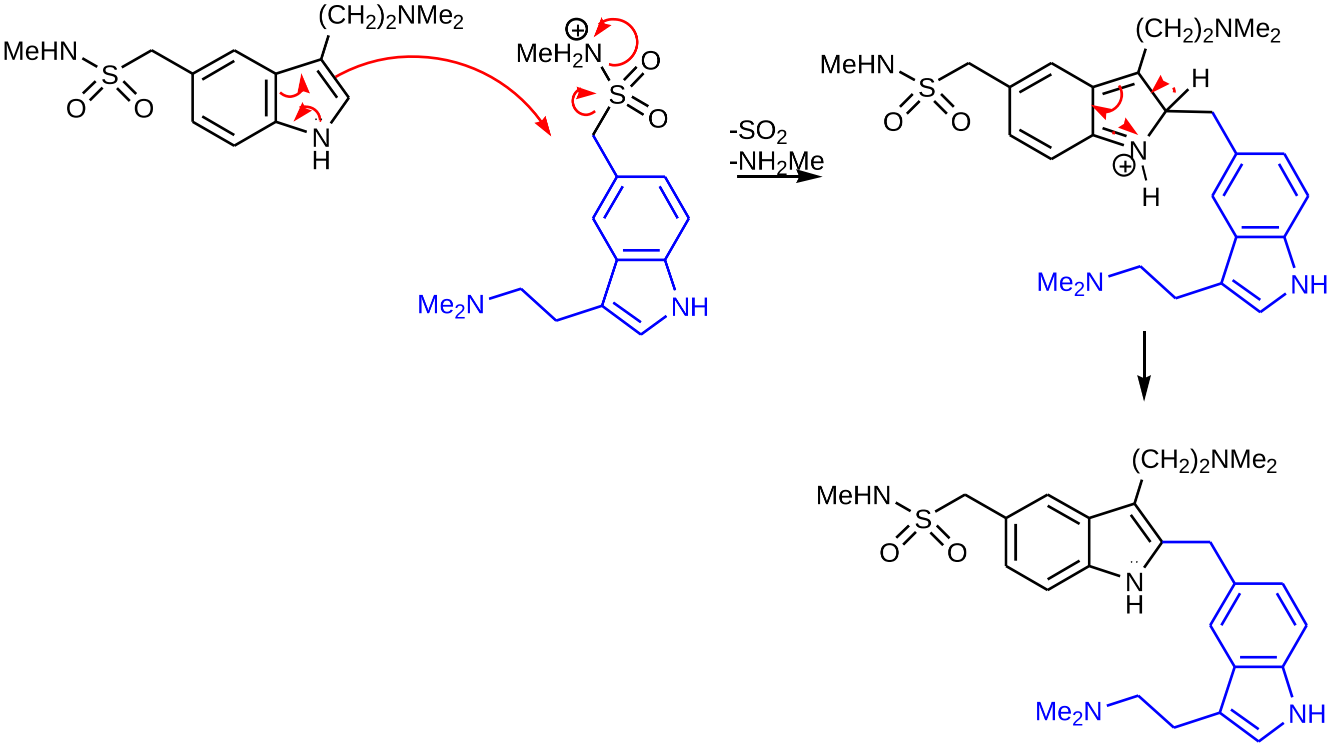
The Fischer Indole synthesis has been used to synthesise the antimigraine agent **sumatriptan** (see figure 10.27). Propose a mechanism by which the two impurities shown in figure 10.28 might have been formed, then suggest how the two ester groups used in figure 10.30 hinder the production of these impurities.

Answer

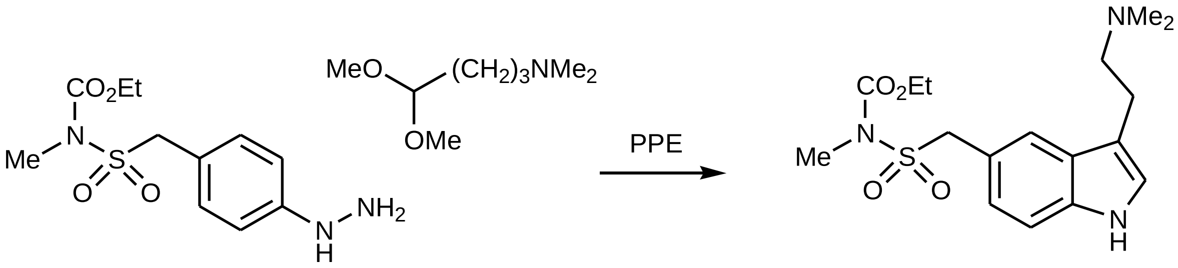
i) Impurity a) is formed when the following reaction is carried out.



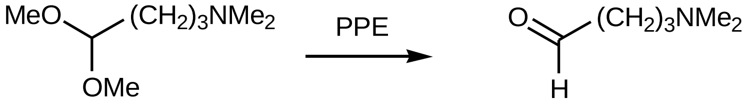
The impurity results from a further reaction where the above product undergoes an electrophilic substitution with a second molecule of product. Note that the amine group in the side chain of the second structure is protonated. This encourages the sulphonamide group to act as a leaving group.



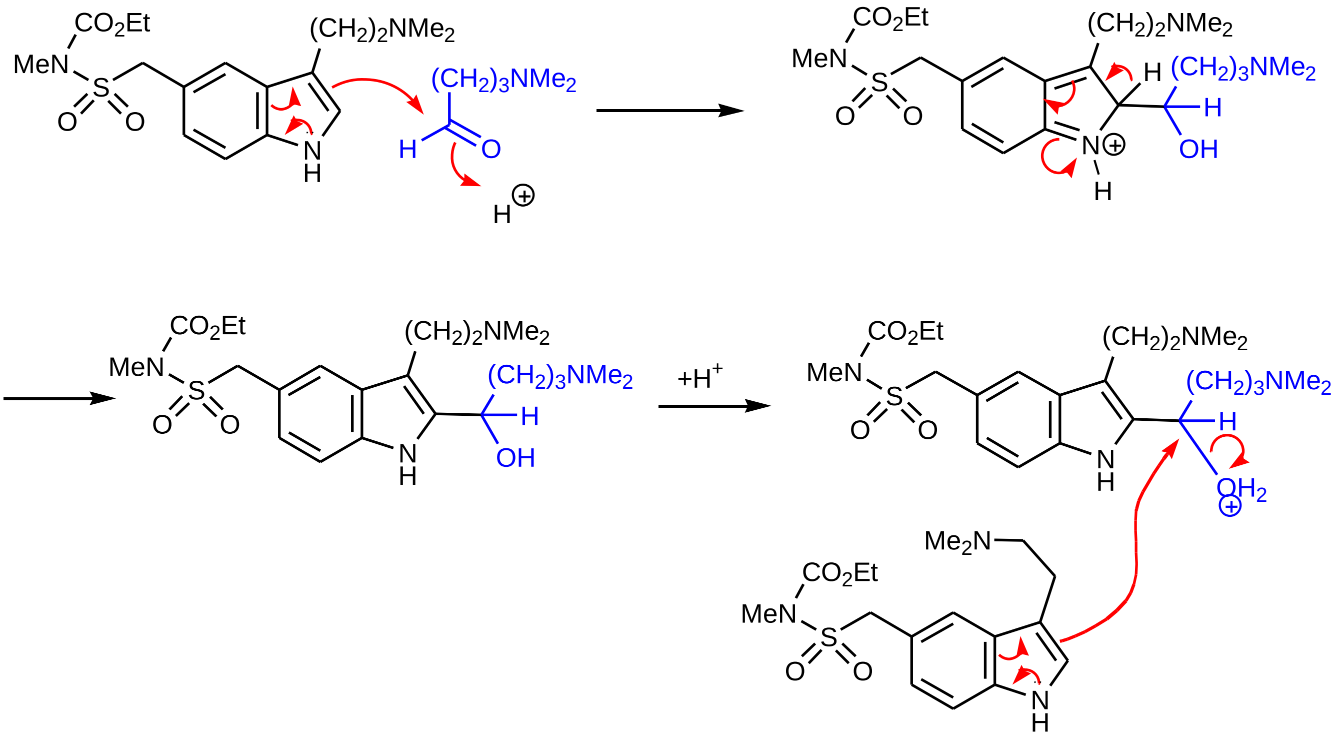
ii) The second impurity (b) is formed during the following reaction.

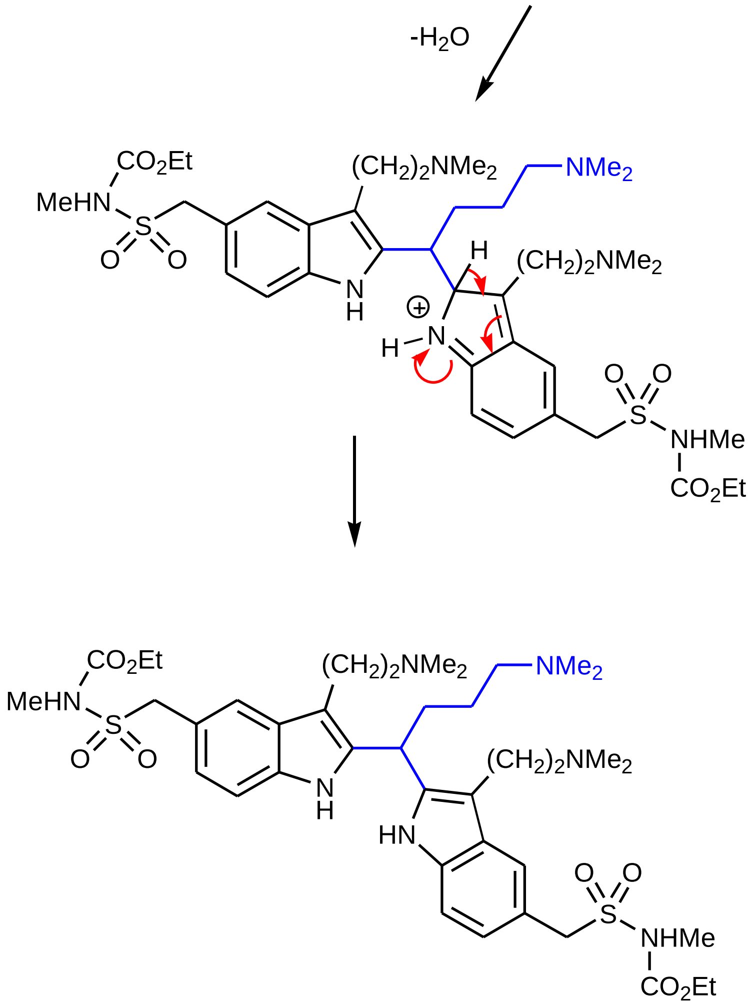


Under acidic conditions, the acetal is converted to an aldehyde which then reacts with the hydrazine to provide the indole.

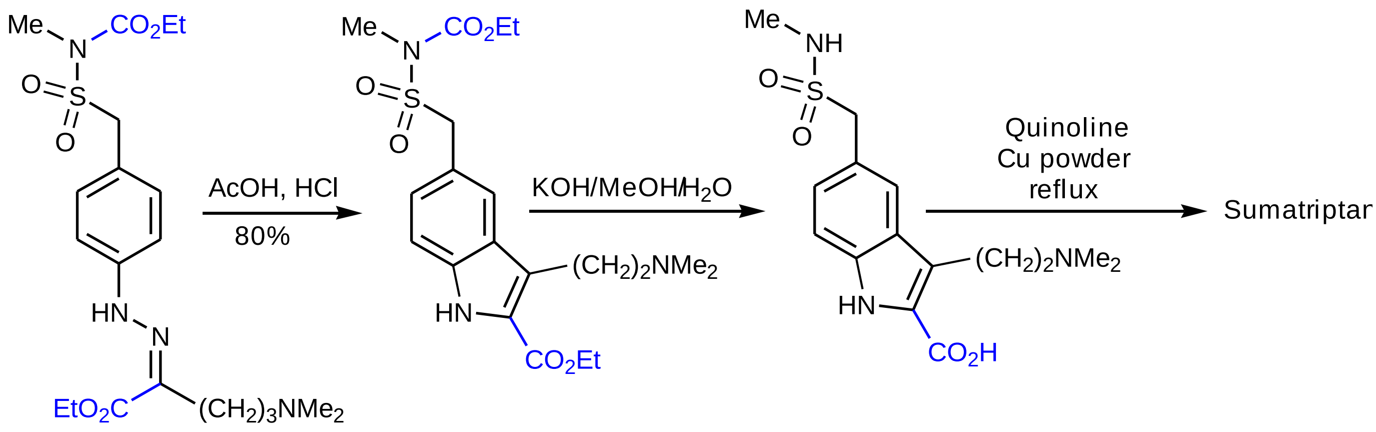


The side reaction involves some of the aldehyde reating with two molecules of product as follows.


CO$_2$Et
MeN
S
O
O
(CH$_2$)$_2$NMe$_2$
N
H
(CH$_2$)$_3$NMe$_2$
H
O
H$^\oplus$
OH
N$^\oplus$
+H$^+$
OH$_2$
Me$_2$N



Both impurities were prevented by using a hydrazone which contained two ester groups shown in blue below. The ester group on the sulphonamide prevents the sulphonamide nitrogen from protonating. As a result, the sulphonamide can no longer act as a leaving group. The ester group on the hydrazone acts as a deactivating group in the final indole product and prevents the product undergoing electrophilic substitution at that position.

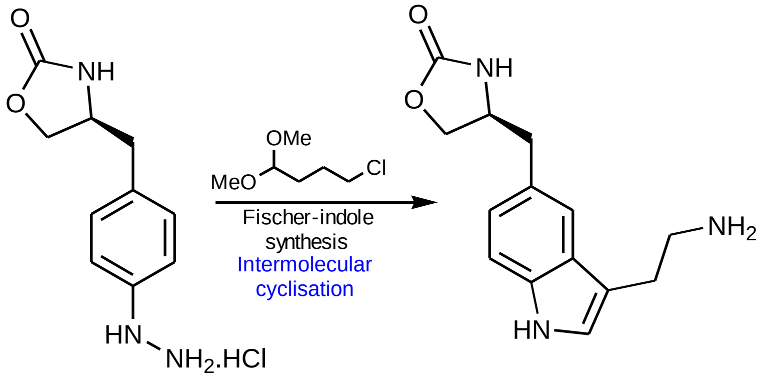


Question 10.9

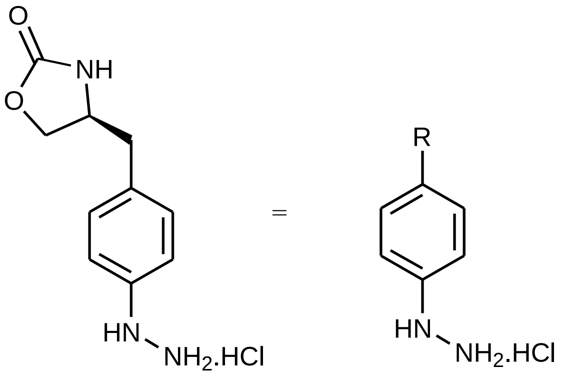
Propose a mechanism by which the product from the Fischer-Indole synthesis shown in figure 10.43 is formed.

Answer

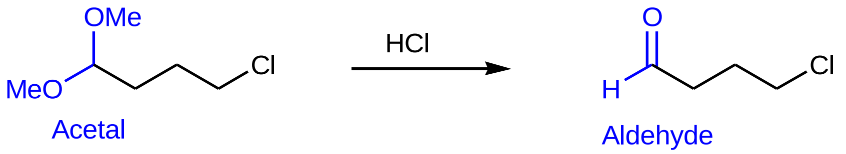
The relevant reaction in figure 10.43 is the following between a hydrazine hydrochloride and an acetal.



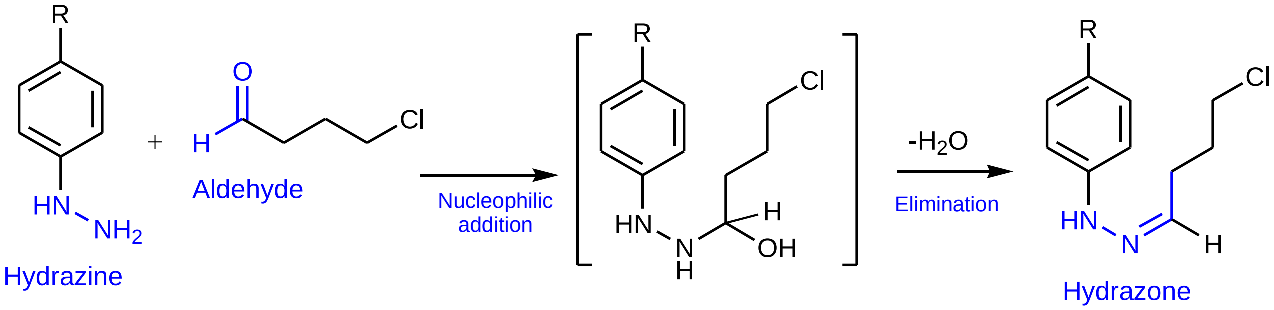
The hydrazine will be represented as follows since the aromatic substituent plays no role in the mechanism.



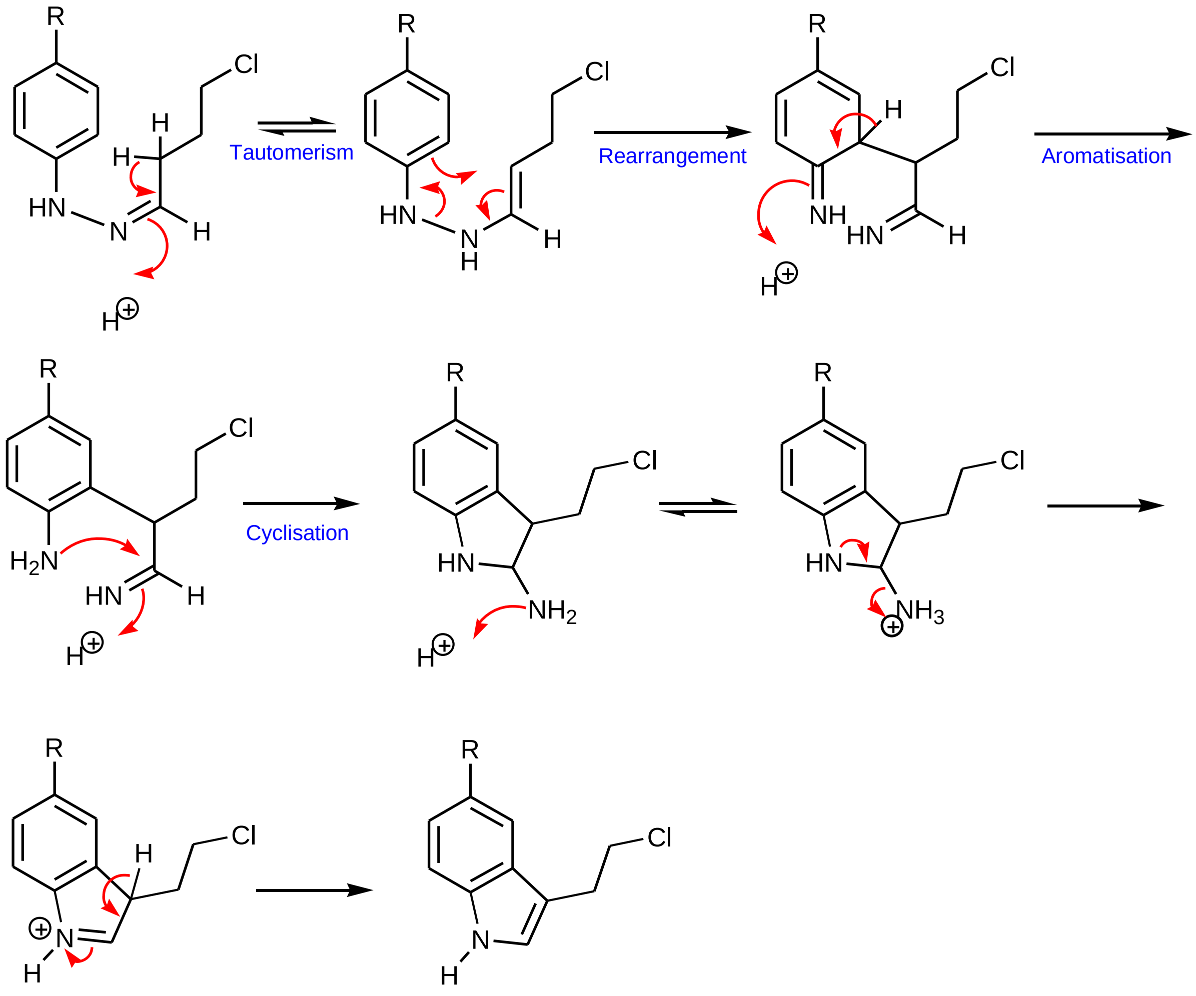
Under acidic conditions, the acetal is converted to an aldehyde.



The hydrazine can now react with the aldehyde through nucleophilic addition and elimination of water to form a hydrazone.



The following mechanism for the cyclisation then ensues.



The indole ring has now been formed, In the process, ammonia has been released and can now act as a nucleophile to substitute the alkyl chloride and give the final product.