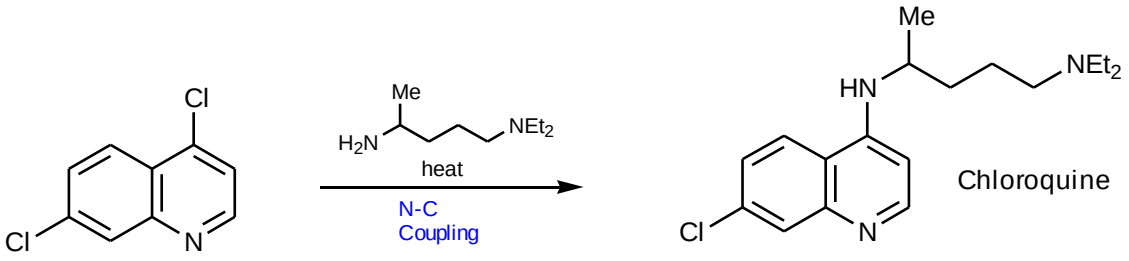
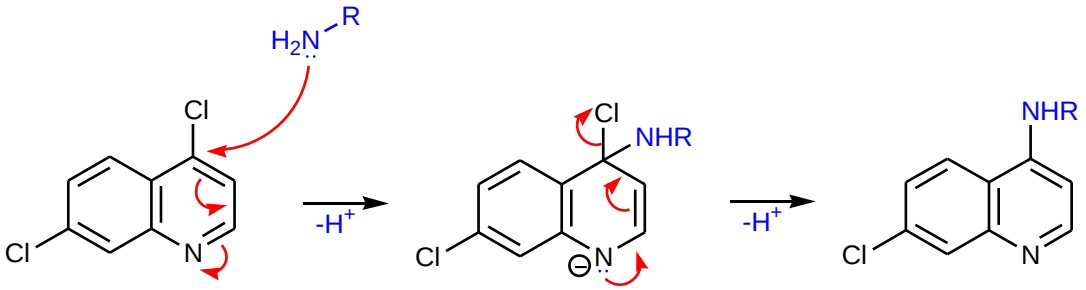
Chapter 2: Drug synthesis

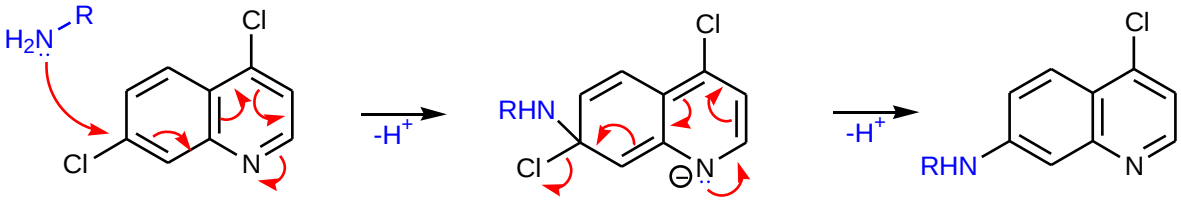
Question 2.1
Explain why the N-C coupling reaction used in the synthesis of the antimalarial agent **chloroquine** displaces one of the chlorine substituents in the bicyclic starting material rather than the other. What kind of selectivity is observed here?



Answer
This is a chemoselective reaction. The nitrogen in the quinoline ring system is responsible for the chemoselectivity. The nitrogen atom is in the correct position to participate in the substitution mechanism as shown below. The negative charge of the intermediate can be placed on the electronegative nitrogen atom where it is more stable than if it was on a carbon atom.



It could be argued that the same stabilisation is possible if the amide reacted with the other chlorine. However, this would require disruption of the aromatic system in both of the bicyclic rings. In the mechanism above, the intermediate still contains an aromatic ring and should be more stable.



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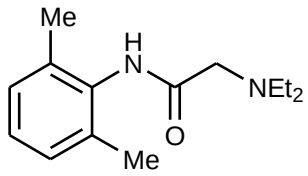
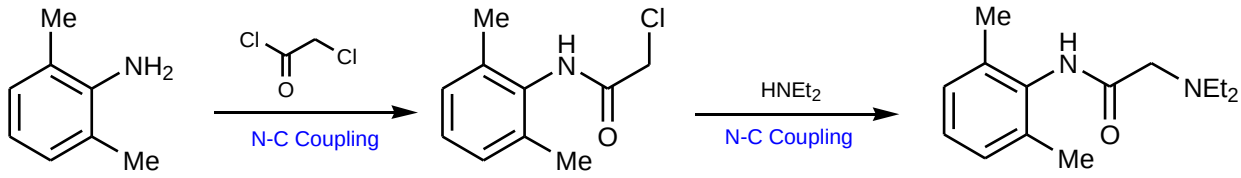
Question 2.2
Suggest how two consecutive coupling reactions could be used to synthesise the local anaesthetic **lidocaine.**



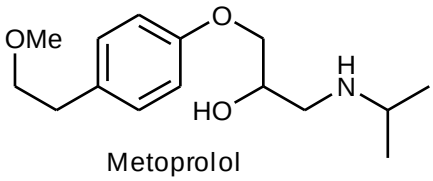
Lidocaine

Answer
Lidocaine can be synthesised from 2-6-dimethylaniline by two consecutive N-C couplings. The first coupling is a nucleophilic substitution of the amine with an acid chloride. The acid chloride is more reactive than the alkyl chloride and so chemoselectivity is possible. The second N-C coupling is a nucleophilic substitution of the alkyl chloride with diethylamine.



Lidocaine

Question 2.3
Suggest how 2 consecutive coupling reactions could be used to synthesise **metoprolol.**



Metoprolol

Answer
A similar synthesis to that used for the synthesis of propranolol can be used (compare Fig. 2.31 in Chapter 2). Note again the chemoselectivity in the first coupling reaction where the alkyl chloride is more reactive than the epoxide.

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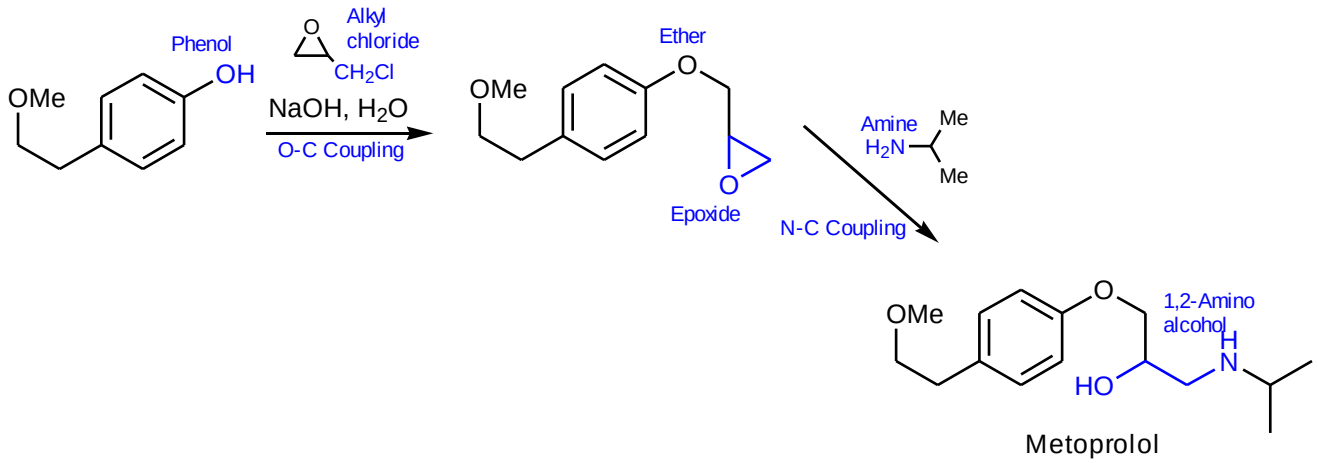
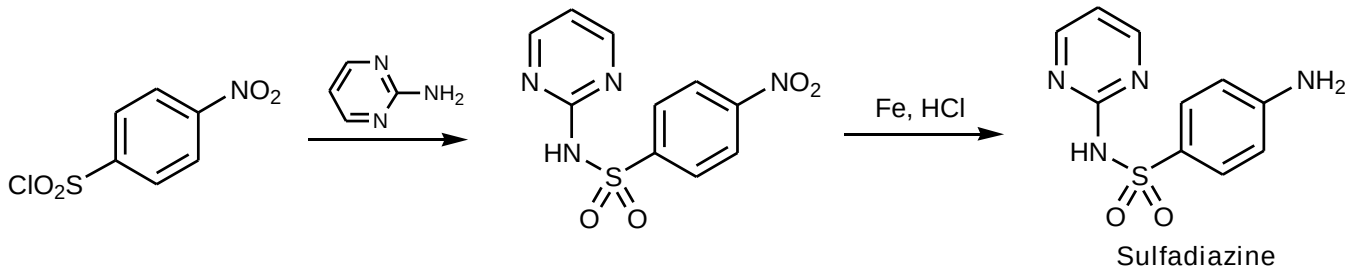
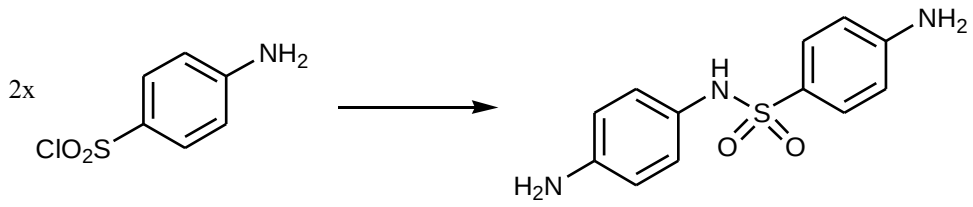


Question 2.4
The synthesis of the antibacterial agent **sulfadiazine** is shown below. Why is a nitro substituent used in the starting material instead of an amine?



Answer
The nitro group is acting as a latent group for the amine group. If an amine group had been present from the beginning then a self condensation would have been possible resulting in an impurity and lowe yields of the desired product.



Question 2.5
In the synthesis of **procaine** shown in figure 2.41, the starting material contains a nitro group which is converted to an amino group at the final stage. Discuss whether the synthesis would have been successful if the reduction of the nitro group had been carried out at the beginning of the synthesis instead of the end.

Answer

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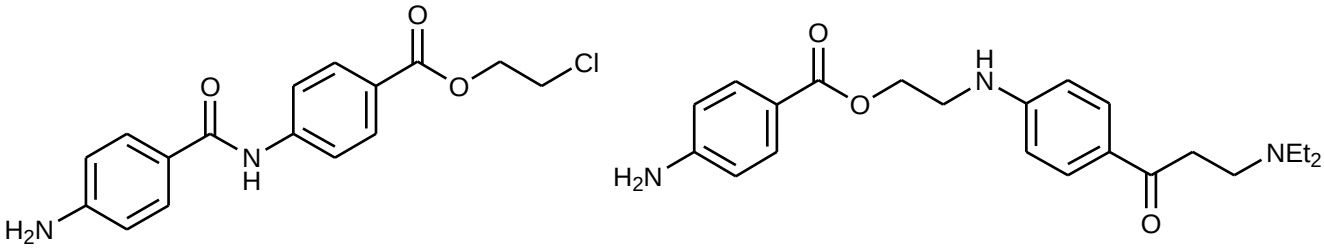
It is unlikely that the synthesis would have been as successful since the amine group could have acted as a nucleophile and competed with the reagents in both coupling reactions to give a number of alternative products. For example, the following might have been formed



Question 2.6
The two reactions shown in figure 2.25 involve an alcohol reacting with an acid chloride, instead of an amine. However, an amine nitrogen is more nucleophilic than an alcohol oxygen. Why do these reactions produce esters rather than amides?

Answer
The first reaction is carried out under acid conditions in order to protonate the amine group as a hydrochloride salt. This means that the nitrogen atom has a positive charge and cannot competer with the alcohol as a nucleophile.
The presence of a base is usual when synthesising an ester from an alcohol and an acid chloride. The base serves to remove the OH proton from a reaction intermediate involved in ester formation. However, this does not explain why the alcohol reacts in preference to the amine. In this case, steric factors may be important. The amine is secondary with the nitrogen nitrogen is linked to a crowded quaternary centre. This may be acting as a steric shield and hindering the amine from acting as a nucleophile. In contrast, the alcohol is primary and is situated at the end of the chain. There is little steric hindance to it acting as a nucleophile.

Question 2.7
A synthesis of the anti-asthmatic agent **montelukast** involved an intermediate (I) containing two alcohol groups, and an intermediate (II) where one of the alcohol groups was protected. Suggest how intermediate (I) could be converted to intermediate II.

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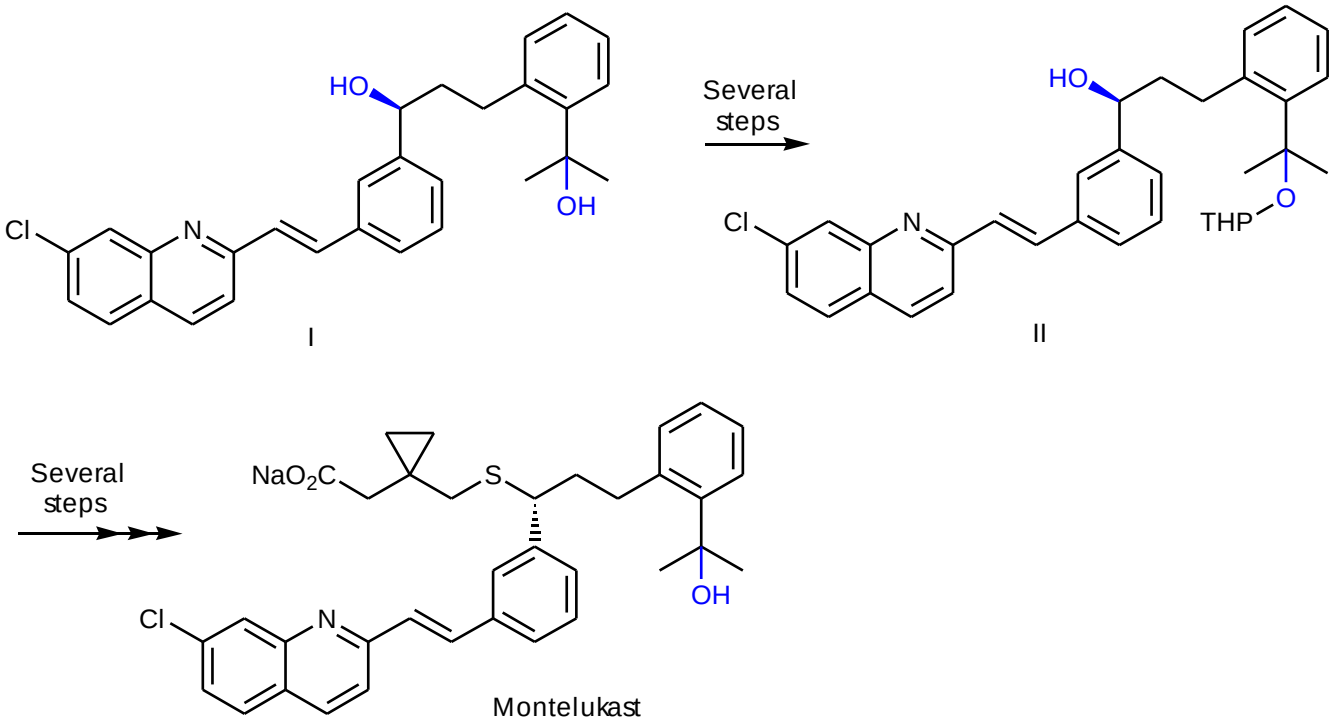

Answer

Chemoselectivity is possible between two similar functional groups if one of the functional groups is more accessible than the other, in which case the more exposed functional group will react more readily. In this example, the more exposed secondary alcohol can be protected selectively with the bulky *tertiary*-butyldimethylsilyl protecting group without reaction at the tertiary alcohol. The selectivity is enhanced by using a bulky silylating agent which differentiates more clearly between the two alcohol groups. The tertiary alcohol can then be protected with a tetrahydropyran group. It is then a case of removing the silyl protecting group selectively. This can be done using tetrabutylammonium fluoride (TBAF).

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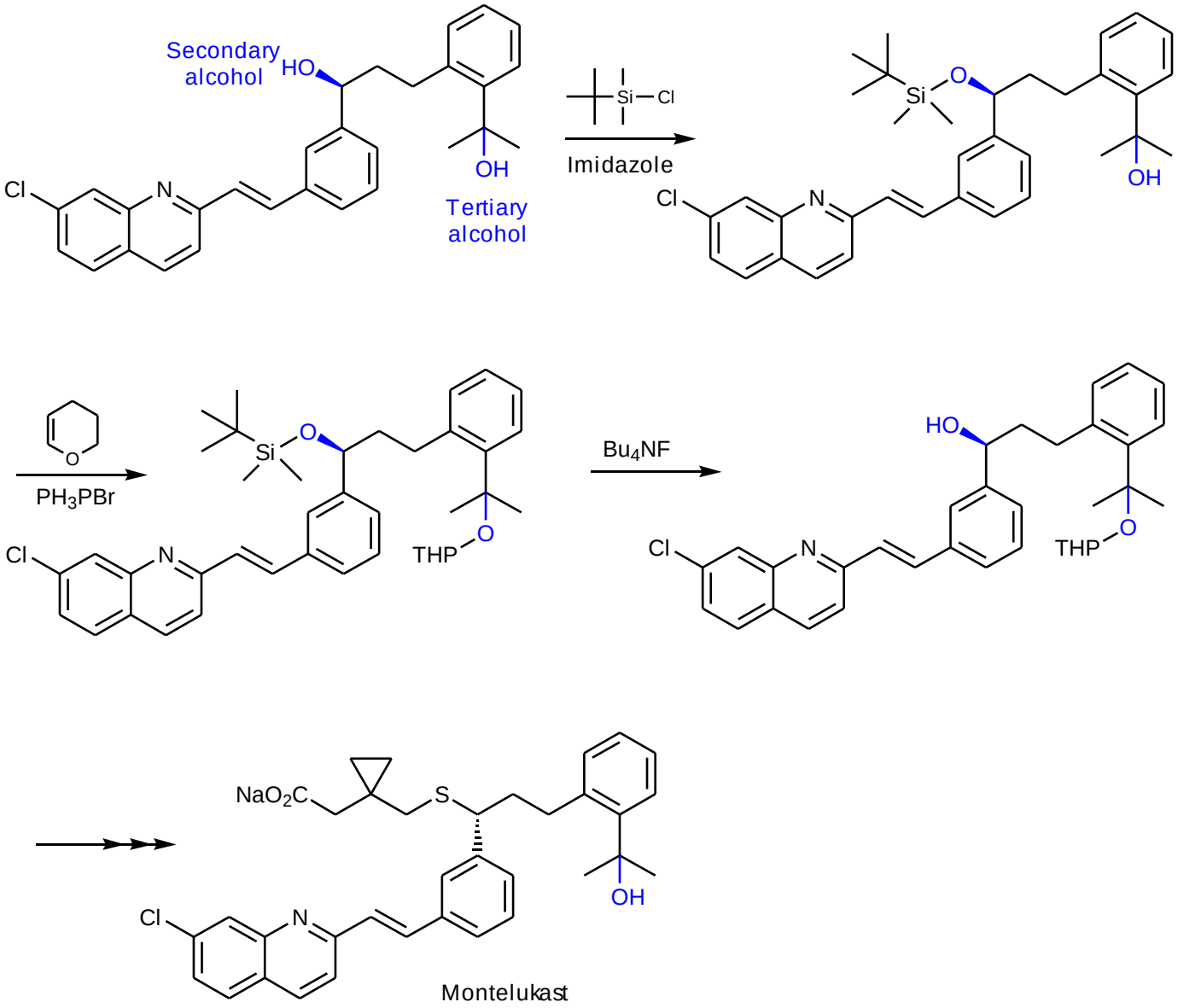

Question 2.8

Pralatrexate is an anticancer agent which can be synthesised as follows. The first stage is a coupling reaction between an amine and a carboxylic acid to give an amide. The amine groups in the bicyclic starting material are not protected, so why do they not react with the carboxylic acid in a self condensation reaction?

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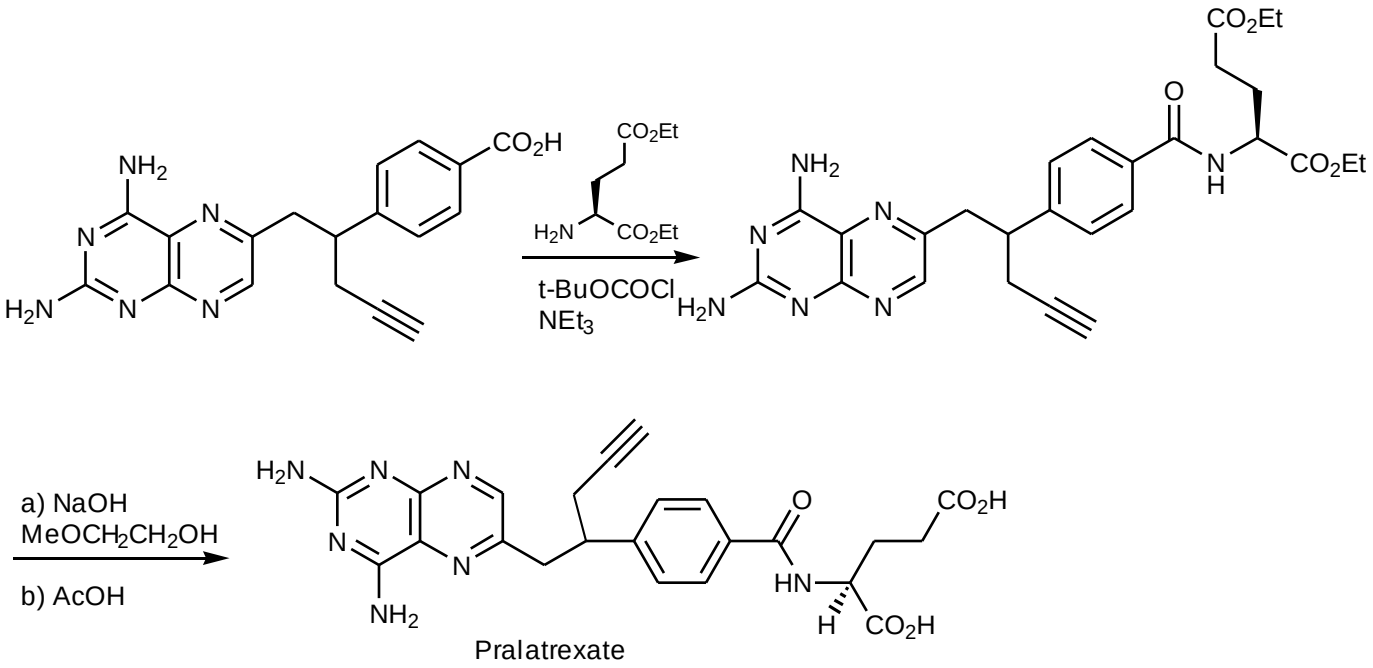
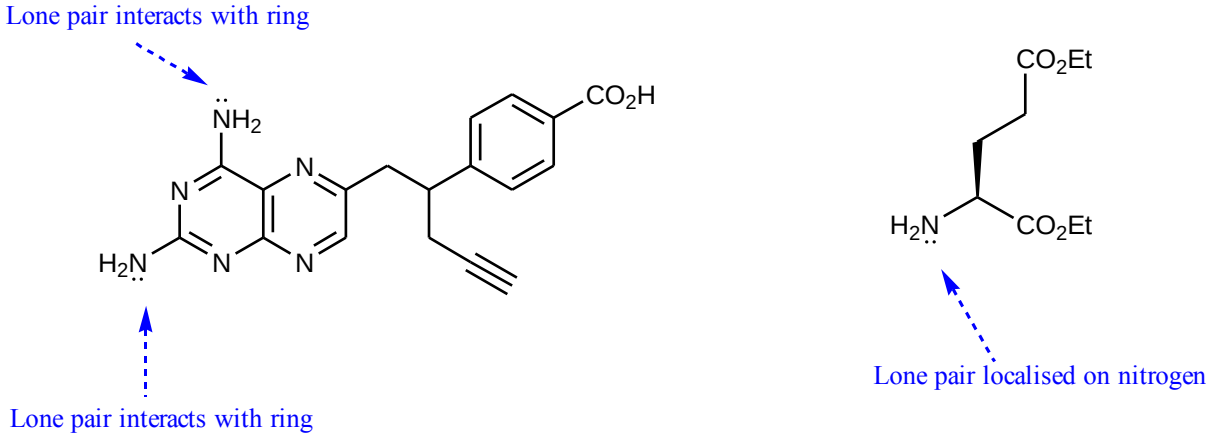


Answer

The amine groups that are present in the starting material are substituents of a heteroaromatic ring system. As a result, they are not very nucleophilic. This is because the lone pairs of the two amine nitrogen atoms can interact with the heteroaromatic ring through resonance. Therefore, both of these amine groups will be much less nucleophilic than the amine group present in the protected amino acid. The lone pair in this case is localised on the nitrogen atom and is much more available to form a bond.



Examples of mechanisms by which the lone pair interacts with the ring.

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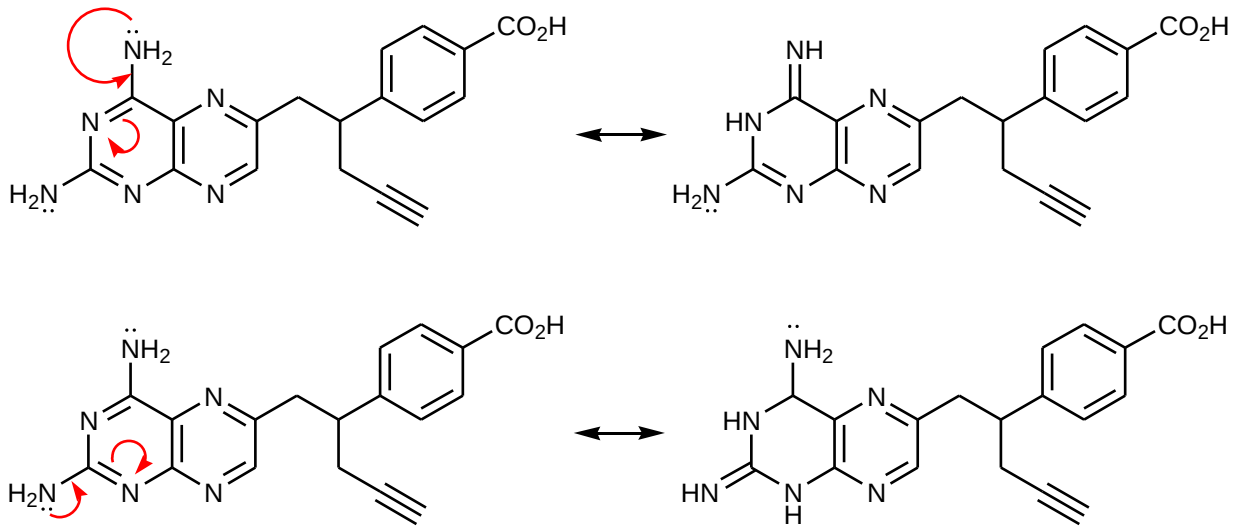
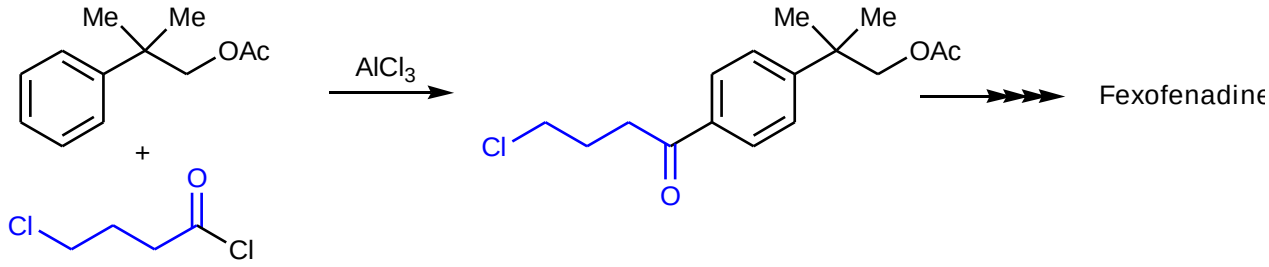


Question 2.9
The following reaction was carried out as one of the early stages in a synthesis of fexofenadine. There is a high regioselectivity for the *para* position over the *ortho* and *meta* positions. Explain the reasons for this selectivity. Identify any chemoselectivity observed in the reaction.



Answer
The reaction is a Friedel Crafts acylation of the aromatic ring with an acid chloride. The reaction is chemoselective since the acid chloride reacts rather than the alkyl chloride, since the acid chloride is more reactive.
There is a substituent already present on the aromatic ring which will affect the regioselectivity of the reaction. There is an ester group present on the side chain, but this is three bonds away from the aromatic ring and will have little influence. Therefore, the substituent will behave like an alkyl substituent in the way it influences the regioselectivity of the Friedel Crafts acylation. This means that it will activate the ring and direct the reaction to the ortho and para positions, rather than the meta position. However, very little ortho substitution takes place despite the fact that there are two ortho positions and only one para position. This is because of the quaternary centre linked directly to the aromatic ring. The two methyl groups act as steric chields and hinder reaction at the ortho positions.

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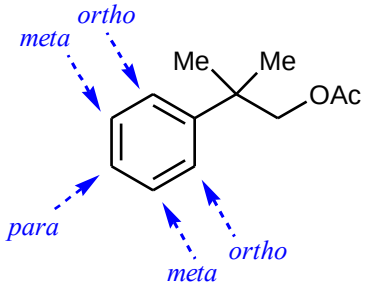

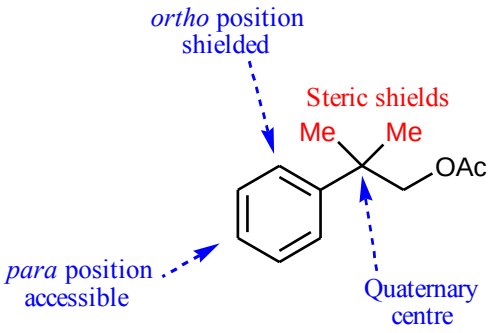

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