# Appendix 4: Coupling Reactions Involving Carbon-Heteroatom Bond Formation

There are a large number of possible methods of coupling molecules through carbon-heteroatom bond formation. The following are examples of the most commonly used C-X couplings in drug synthesis.

## App 4.1 Synthesis of amides

Amide formation is one of the most common reactions carried out in drug synthesis. Secondary and tertiary amides are relatively common in drugs, whereas primary amides are less common. The tetracyclines are one example of a class of drugs containing a primary amide group.

### App 4.1.1 Conversion of acid chlorides, acid anhydrides or esters to amides

Amides can be prepared by the reaction of an amine with an acid chloride by nucleophilic substitution (Fig. 1a). Treatment of the acid chloride with ammonia gives a primary amide, treatment with a primary amine gives a secondary amide and treatment with a secondary amine gives a tertiary amide. Tertiary amines cannot be used in this reaction because they do not give a stable product.
Two equivalents of amine are required for the reaction since one equivalent of the amine is used up in forming a salt with the hydrochloric acid that is produced as a by product. This is clearly wasteful on the amine, especially if the amine is expensive and not easily synthesised. To avoid this, one equivalent of sodium hydroxide or pyridine can be added to the reaction in order to neutralize the HCl produced.

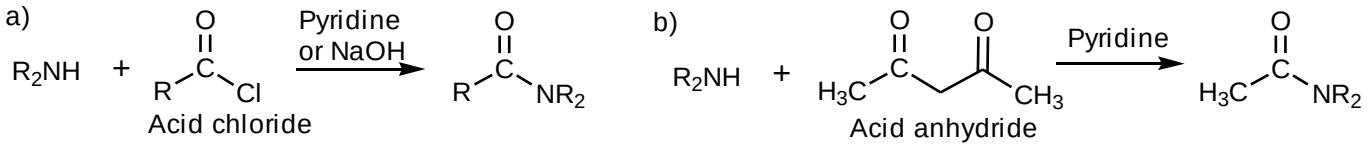


**Figure 1** Reactions of amines with carboxylic acid derivatives.

Amides can also be synthesized from acid anhydrides and esters, but in general these reactions offer no advantage over acid chlorides since acid anhydrides and esters are less reactive. Furthermore, with acid anhydrides half of the parent carboxylic acid is lost as the leaving group. This is wasteful and so acid anhydrides are only used for the synthesis of amides if the acid anhydride is cheap and freely available (e.g. acetic anhydride) (Fig. 1b).

### App 4.1.2 Coupling an amine with a carboxylic acid to form an amide

The synthesis of amides directly from carboxylic acids and amines is not straightforward since an acid-base reaction is more likely to take place to form a salt. Therefore, an activating or coupling agent is used to promote the reaction. One of the most popular coupling agents is dicyclohexylcarbodiimide (DCC). This structure reacts with the carboxylic acid to form an activated intermediate, which then reacts with the amine (Fig. 2). This procedure is commonly used in peptide synthesis, but there can be problems with side reactions and epimerisation. These problems can be eased to a large extent by adding a further reagent called 1-hydroxybenzotriazole (HOBt). This

reagent reacts with the activated intermediate to form a second intermediate which then reacts with the amine with less risk of epimerisation.

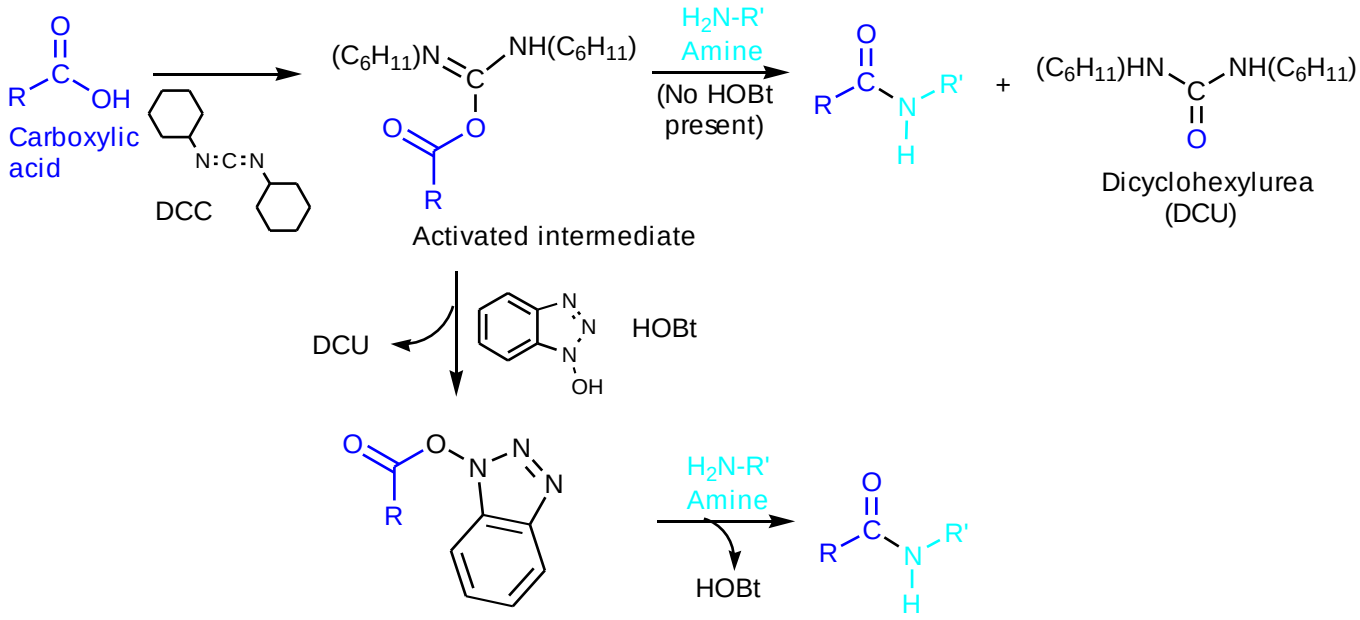


**Figure 2** Coupling of an amine with a carboxylic acid in the presence of dicyclohexylcarbodiimide (DCC).

Another problem with the use of DCC is the formation of dicyclohexylurea which is poorly soluble and difficult to remove. An alternative coupling agent is diisopropylcarbodiimide (DIC) ($Me_2HC$-N=C=N-$CHMe_2$) which forms a urea (DIU) which is soluble in dichloromethane. This makes it a better choice for solid phase coupling reactions. A vast number of other coupling agents have been studied and used in amide formation, including 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (Et-N=C=N-$(CH_2)_3$-$NMe_2$), which is a water-soluble coupling agent.
The coupling agents benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) and bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP) are commonly used in solid phase synthesis to carry out coupling reactions.

**App 4.1.3 Methylation of secondary amides to form tertiary amides**
Secondary amides can be treated with sodium hydride to deprotonate the amide, then methylated with iodomethane to give an *N*-methylated tertiary amide (Fig. 3). This feature is present in several drugs that have been derived from peptide lead compounds. The presence of the *N*-methyl group can prevent peptidases catalysing the hydrolysis of the original amide or peptide bond.

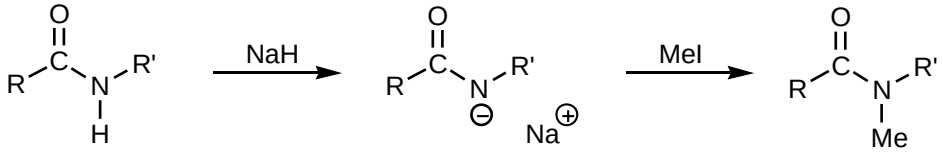

**Figure 3** *N*-Methylation of secondary amides.

## App 4.2 Synthesis of Amines

Amines can be synthesised from alkyl halides, amides, acid chlorides, ketones, & aldehydes.

### App 4.2.1 Conversion of alkyl halides to primary amines via azides

Primary alkyl halides can undergo nucleophilic substitution with an azide ion (Fig. 4). The resulting azide can then be reduced by $LiAlH_4$ or by catalytic hydrogenation to a primary amine. Another method of reduction is to use triphenylphosphine or tributylphosphine in a method called the **Staudinger reaction**. Some secondary alkyl halides can be converted to amines in a similar manner.

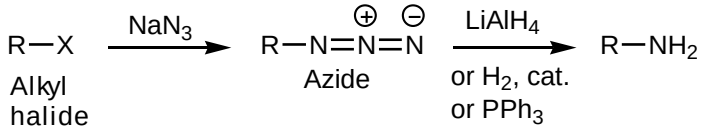


**Figure 4** Conversion of a primary alkyl halide to a primary amine.

### App 4.2.2 Conversion of alkyl halides to primary amines

Another method of achieving the same result is the **Gabriel synthesis** of amines (Fig. 5). This involves treating phthalimide with KOH to abstract the N-H proton. The phthalimide ion can then be alkylated by treating it with an alkyl halide in a nucleophilic substitution. Subsequent hydrolysis releases a primary amine. An alternative method of releasing the primary amine is to cleave the substituted phthalimide with hydrazine.

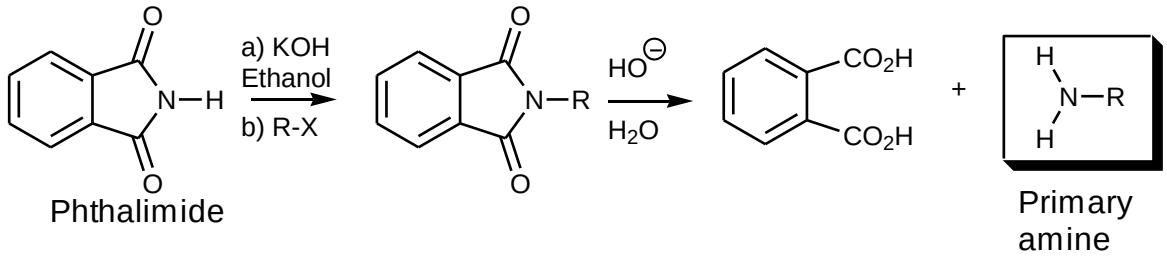


**Figure 5** Gabriel synthesis of amines.

### App 4.2.3 Rearrangements of carboxylic acid derivatives to primary amines

There are two rearrangement reactions which can be used to convert carboxylic acid derivatives into primary amines, where the carbon chain in the product has been shortened by one carbon unit (Fig. 6). These are known as the Hofmann and the Curtius rearrangements. The Hofmann rearrangement involves the treatment of a primary amide with bromine under basic conditions, while the Curtius rearrangement involves heating an acyl azide. The end result is the same - a primary amine with loss of the original carbonyl group.

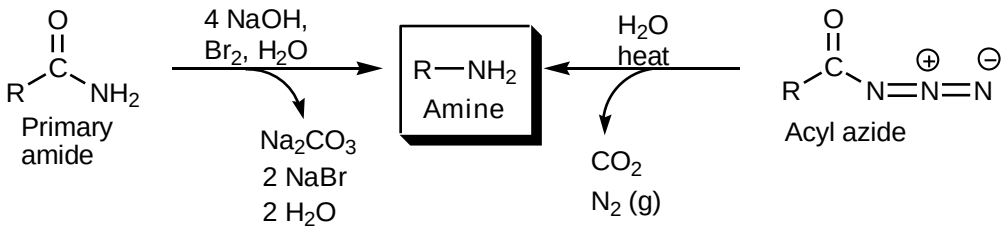


**Figure 6** Hoffmann and Curtius rearrangements.

In both reactions, the alkyl group (R) is transferred from the carbonyl group to the nitrogen to form an intermediate isocyanate (O=C=N-R). This is then hydrolyzed by water to form carbon dioxide and the primary amine. The Curtius rearrangement has the added advantage that nitrogen is lost as a gas, which helps to drive the reaction to completion.

### App 4.2.4 Alkylation of amines

Ammonia, primary amines and secondary amines can undergo the $S_N2$ reaction with alkyl halides to produce a range of primary, secondary and tertiary amines. The amines are produced as aminium salts which are converted to the free amine by treatment with sodium hydroxide (Fig. 7a).

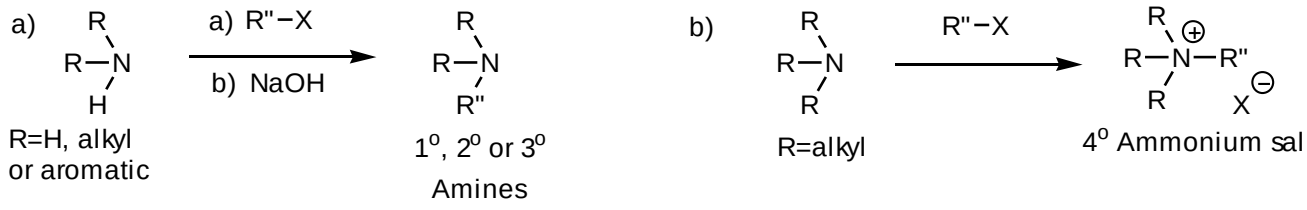


**Figure 7** Alkylation of amines.

In theory, it should be possible to synthesize primary amines from ammonia, secondary amines from primary amines, and tertiary amines from secondary amines. In practice, over-alkylation is common. For example, reaction of ammonia with methyl iodide leads to a mixture of primary, secondary, and tertiary amines along with a small quantity of the quaternary ammonium salt (Fig. 8).

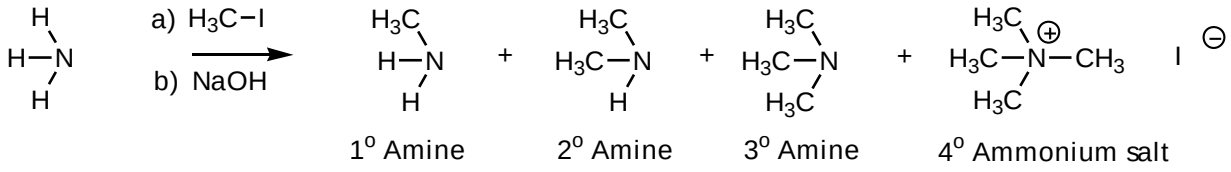


**Figure 8** Over-alkylation of ammonia.

Alkylation of tertiary amines by this method is a good way of obtaining quaternary ammonium salts (Fig. 7b) since no other products are possible. However, alkylation of lower order amines is not so satisfactory. One way round this problem is to acylate the amine to form an amide then reduce the amide to an amine (Fig. 9). Acylation can only occur once. Despite the problems of *N*-alkylation, it is one of the most frequently used reactions carried out in drug synthesis.

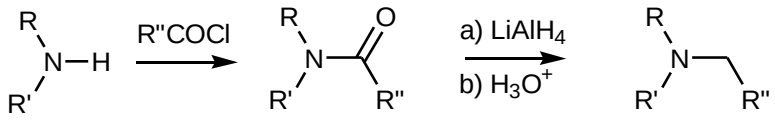


**Figure 9** Alternative method of adding an alkyl substituent.

**App 4.2.5 Alkylating an amine by reductive amination of ketones or aldehydes**

Another method of alkylating a primary or secondary amine is to treat the amine with a ketone or an aldehyde in the presence of the reducing agent sodium cyanoborohydride (Fig. 10). This reaction is known as a reductive amination and is one of the most common reactions used in drug synthesis. The reaction proceeds through an imine or an iminium ion which is reduced *in situ*. Over alkylation cannot occur by this method. $NaBH_4$ and $LiAlH_4$ have also been used as the reducing agent.

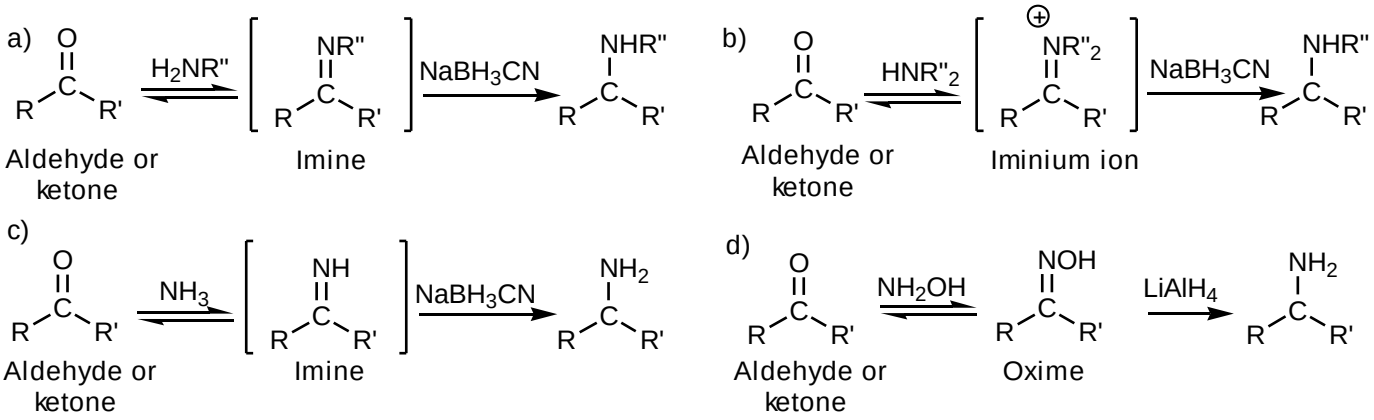


**Figure 10** Reductive aminations of carbonyl compounds.

Primary amines are converted to secondary amines (Fig 10a) and secondary amines are converted to tertiary amines (Fig. 10b). The reaction is also suitable for the synthesis of primary amines if ammonia is used instead of an alkylamine. In this case, the imine intermediate is unstable and so the reduction should be carried out without isolating the imine (Fig. 10c). An alternative method for synthesising primary amines is to use hydroxylamine instead of ammonia. The resulting oxime is reduced to the amine by $LiAlH_4$ or by hydrogenation (Fig. 10d).

Reductive amination has an advantage over the 2-stage acylation and reduction of an amine described in figure 11 as a branched alkyl group can be added (Fig. 11).

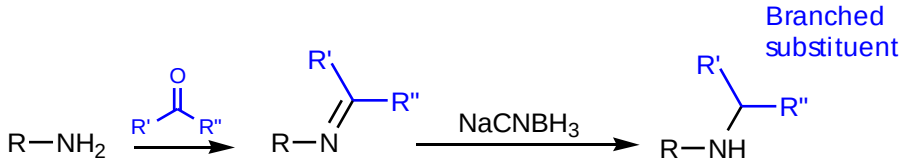


**Figure 11** Reductive amination of a ketone to add a branched substituent.

### App 4.2.6 Palladium-catalysed aminations of aromatic rings

Palladium-catalysed aminations have been used successfully to couple a primary or secondary amine with an aromatic or heteroaromatic ring (Fig. 12a). An aryl halide is used as starting material and the halogen is eventually replaced with an amine substituent.

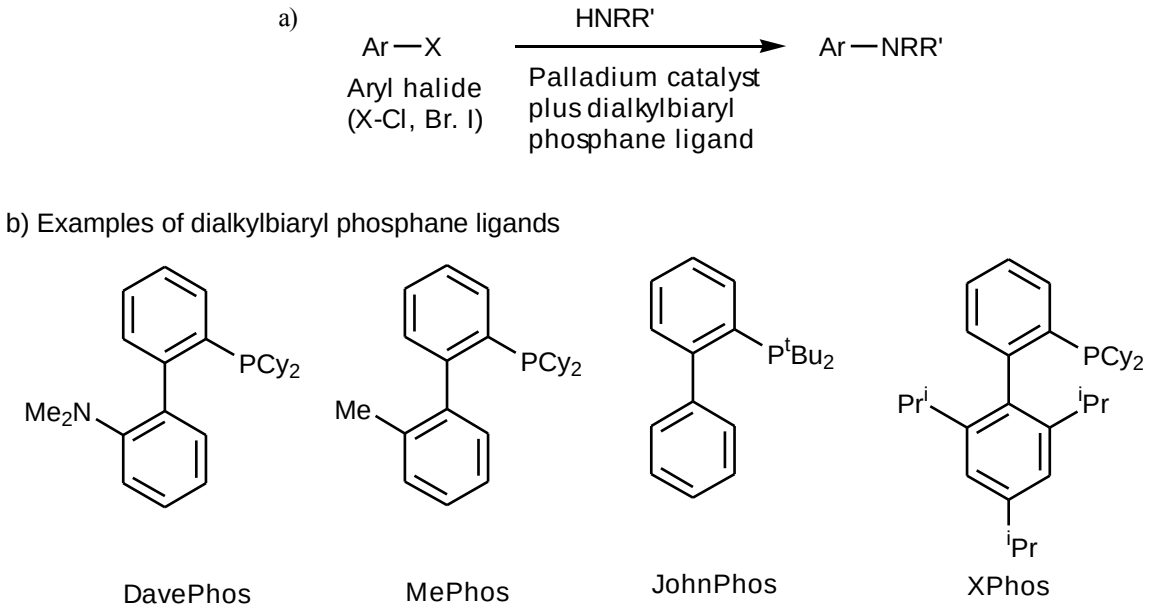


**Figure 12** a) Palladium-catalysed aminations b) Examples of dialkylbiaryl phosphane ligands.

A dialkylbiaryl phosphane ligand is required and the nature of the ligand plays an important role in allowing the reaction to be carried out under mild conditions. The ligand also serves to shorten the reaction time, and lower the amount of catalyst required. There are a large variety of these ligands now available (Fig. 12b).

## App 4.3 Synthesis of enamines

Enamines can be formed by the reaction of a secondary amine with an aldehyde or ketone, as long as there is an α-proton present in the aldehyde or ketone (Fig. 13). This proton is lost in order to form the enamine, and an acid catalyst is usually required. The yield can be improved by adding a dehydrating agent such as titanium tetrachloride to remove the water that is formed from the reaction. With unsymmetrical ketones, there is the possibility of two different enamines, in which case the more stable enamine is preferred.

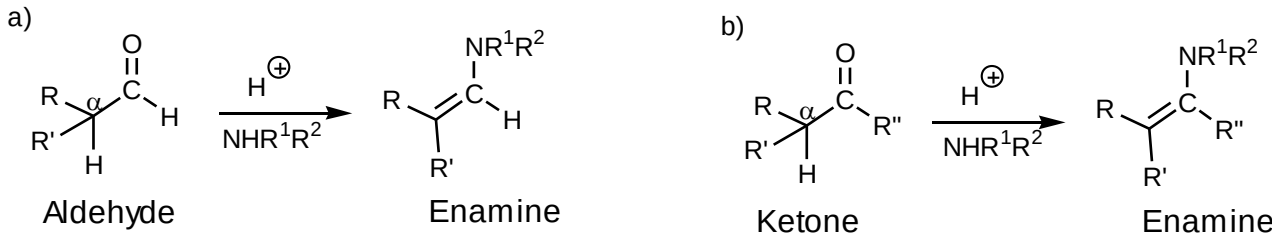

**Figure 13** Enamines from reaction of a secondary amine with a) an aldehyde or b) a ketone.

## App 4.4 Synthesis of esters

There are many different ways in which esters can be synthesized.

### App 4.4.1 Esters from the reaction of alcohols with acid chlorides or acid anhydrides

A very effective method of synthesis is to react an acid chloride with an alcohol in the presence of pyridine (Fig. 14a). Acid anhydrides also react with alcohols to give esters, but are less reactive. Furthermore, the reaction is wasteful since half of the acyl content in the acid anhydride is lost as the leaving group (i.e. the carboxylate ion). This is not a problem if the acid anhydride is cheap and readily available. For example, acetic anhydride is useful for the synthesis of a range of acetate esters (Fig. 14b).

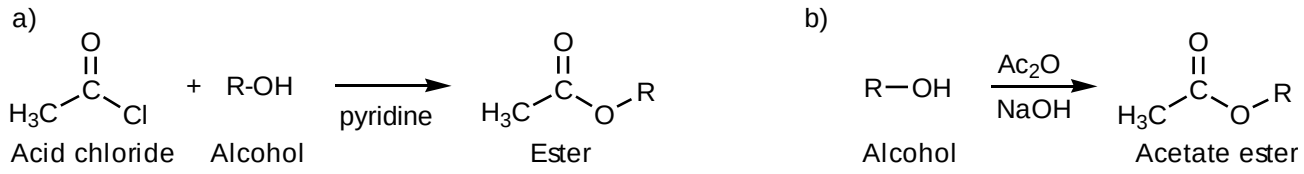


**Figure 14** Synthesis of esters from alcohols reacting with acid chlorides or acid anhydrides.

### App 4.4.2 Synthesis of esters from carboxylic acids

A very common method of synthesizing esters is to treat a carboxylic acid with an alcohol in the presence of a catalytic amount of a mineral acid (Fig. 15a), while an excellent method of preparing methyl esters is to treat carboxylic acids with diazomethane (Fig. 15b). Good yields are obtained in the latter reaction because nitrogen is formed as one of the products and is lost as a gas, thus driving the reaction to completion. However, diazomethane is an extremely hazardous chemical which can explode, and strict safety precautions are necessary when using it.

A carboxylic acid can also be converted to a carboxylate ion and then treated with an alkyl halide (Fig. 15c). The reaction involves the $S_N2$ nucleophilic substitution of an alkyl halide and so the reaction works best with primary alkyl halides.

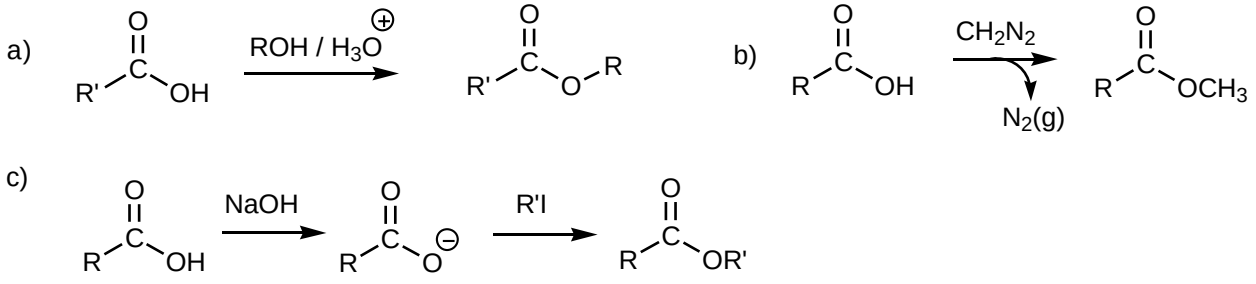


**Figure 15** Synthesis of esters from carboxylic acids.

Another method of creating esters from carboxylic acids is through the **Mitsunobu reaction** where the carboxylic acid is reacted with an alcohol in the presence of triphenylphosphine ($PPh_3$) and diethyl azodicarboxylate - the latter reagent being given the ominous acronym (DEAD) (Fig. 16). DEAD serves to activate triphenylphosphine such that it becomes linked to the alcohol group to form an alkoxyphosphonium salt containing a strong oxygen-phosphorus bond. The carboxylic acid is also converted to a carboxylate ion which then carries out a nucleophilic substitution reaction on the alkoxyphosphonium salt to give the ester product. Although the carboxylate ion is a poor nucleophile, the reaction is driven by the formation of triphenylphosphine oxide which contains a very strong P=O bond. The reaction can be classed as a redox reaction since DEAD is reduced and triphenylphosphine is oxidised as a result of the mechanism. Note that an inversion of configuration takes place for chiral alcohols, which would not occur with the methods previously described.

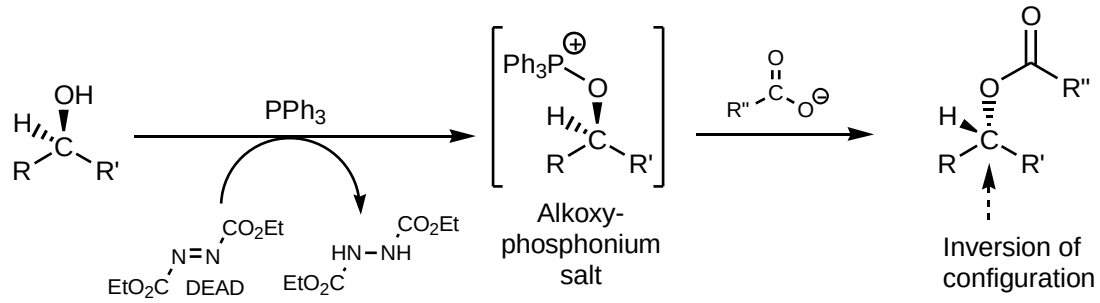


**Figure 16** Synthesis of esters by the Mitsunobu reaction.

### App 4.4.3 Esters by transesterification

Esters can be converted by nucleophilic substitution from one type of ester to another - a process called transesterification. For example, a methyl ester can be dissolved in ethanol in the presence of an acid catalyst and converted to an ethyl ester (Fig. 17a). The reaction is an equilibrium reaction, but when an alcohol is used as solvent, it is in large excess and the equilibrium is shifted to the desired ester. Furthermore, if the alcohol to be replaced has a low boiling point, it can be distilled from the reaction as it is formed, thus shifting the equilibrium further to the desired product.


**Figure 17** Synthesis of esters by a) transesterification and b) hydrolysis of nitriles.

### App 4.4.4 Phenyl esters

Phenols (ArOH) can be converted into phenyl esters (ArOCOR) by reaction with acid chlorides or acid anhydrides. However, unlike alcohols, phenols are not converted to esters by reaction with a carboxylic acid under acid catalysis.

### App 4.4.5 Hydrolysis of nitriles to esters

Nitriles (RCN) can be hydrolyzed to esters by reaction with an alcohol under acid conditions (Fig. 17b).

### App 4.4.6 Synthesis of esters by the Baeyer Villiger oxidation of ketones

Treatment of a ketone with a peroxy acid leads to the synthesis of an ester where one of the alkyl groups of the original ketone migrates to the oxygen of the ester (Fig. 18). With unsymmetrical ketones, there are two possible products, depending on which alkyl group migrates. However, there is a marked preference between different types of migratory groups, which follows the order tertiary > secondary > benzyl > aryl > primary > Me. Chiral groups retain their absolute configuration when they migrate.

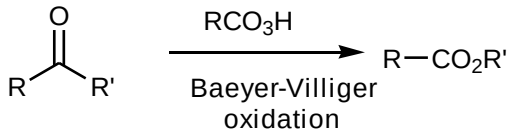


**Figure 18** The Baeyer-Villiger oxidation of ketones.

## App 4.5 Synthesis of ethers

### App 4.5.1 Aliphatic ethers from alcohols and alkyl halides

The Williamson ether synthesis is the best method of preparing aliphatic ethers (Fig. 19a). The procedure involves the $S_N2$ reaction between a metal alkoxide and a primary alkyl halide or tosylate. The alkoxide required for the reaction is prepared by treating an alcohol with a strong base such as sodium hydride or metallic sodium. An alternative procedure is to treat the alcohol directly with the alkyl halide in the presence of silver oxide, thus avoiding the need to prepare the alkoxide beforehand.

If an unsymmetrical ether is being synthesized, the most hindered alkoxide should be reacted with the simplest alkyl halide, rather than the other way round. Since this is an $S_N2$ reaction, primary alkyl halides react better then secondary or tertiary alkyl halides.

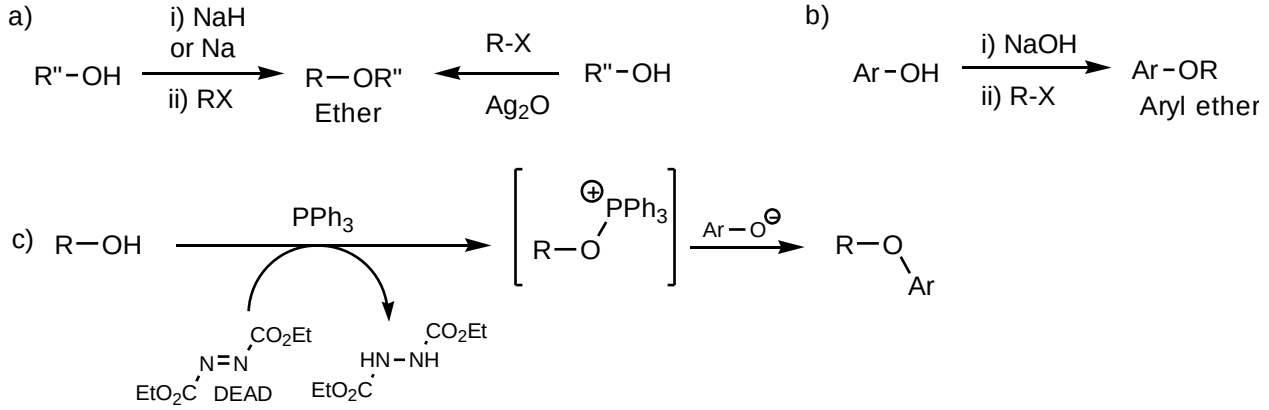


**Figure 19** Synthesis of ethers from alkyl halides and alcohols.

**App 4.5.2 Aromatic ethers from the reaction of phenols with alkyl halides or alcohols**

Phenols can be converted into aryl ethers by reaction with alkyl halides in the presence of base (Fig. 19b**)**. The reactions can be carried out under milder conditions than those used for alcohols due to the greater acidity of phenols. Thus, phenols can be converted to phenoxide ions with sodium hydroxide rather than metallic sodium. Dimethyl sulphate can be used instead of iodomethane to form aromatic methyl ethers.

Another method of alkylating phenols is to carry out the reaction with an alcohol in the presence of triphenylphosphine and diethyl azodicarboxylate in a **Mitsunobu coupling** (Fig. 19c;).

**App 4.5.3 Aliphatic ethers from alcohols and alkenes**

Alkenes can be converted to ethers by the electrophilic addition of mercuric trifluoroacetate, followed by addition of an alcohol (Fig. 20). An organomercuric intermediate is obtained which can be reduced with sodium borohydride to give the ether.

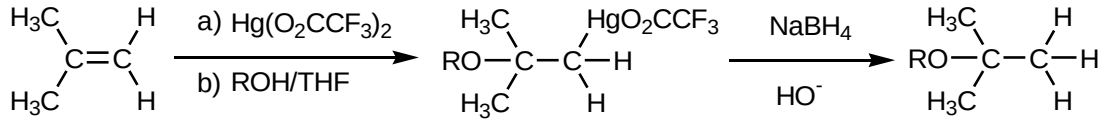


**Figure 20** Synthesis of ethers from alkenes and alcohols.

## App 4.6 Synthesis of imines

The reaction of primary amines with aldehydes and ketones in the presence of an acid catalyst generates imines which are also known as **Schiff bases** (Fig. 21). Water is formed as a by-product and can be removed by heating the reaction to reflux such that the water is azeotroped off into a Dean and Stark apparatus, or absorbed by molecular sieves held in a soxhlet apparatus. Alternatively, trimethylorthoformate can be used as a dehydrating solvent without the need for acid catalysis.

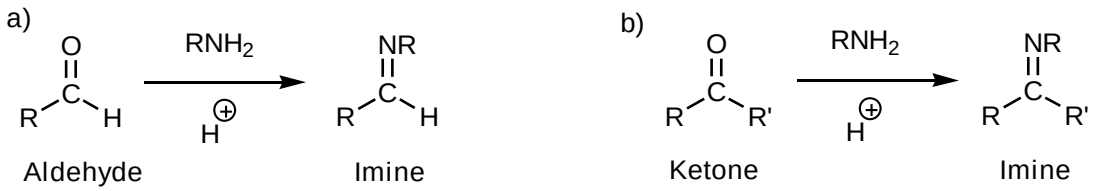


**Figure 21** Formation of imines from aldehydes and ketones with amines.

## App 4.7 Synthesis of oximes and oxime ethers

Oximes can be prepared by the reaction of aldehydes or ketones with hydroxylamine (Fig. 22). *O*-Alkylation can be achieved with diazomethane, alkyl halides or alkyl sulphates to give the oxime ethers.

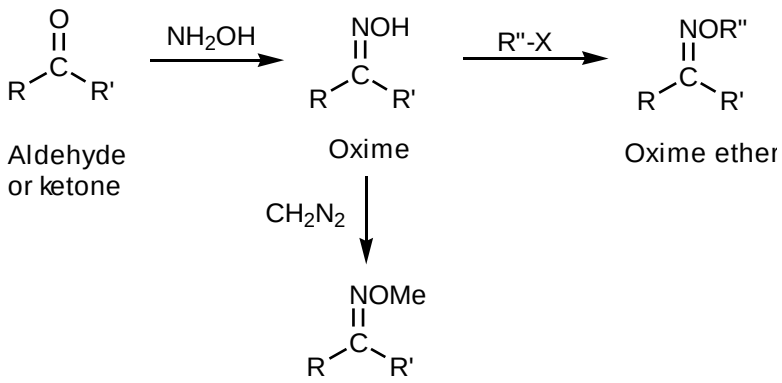


**Figure 22** Synthesis of oximes and oxime ethers from aldehydes and ketones.

## App 4.8 Synthesis of sulphonamides

Sulphonamides can be formed by reacting primary and secondary amines with a sulphonyl chloride in the presence of pyridine (Fig. 23). Tertiary amines do not give a stable product and are recovered unchanged. The reaction works for both aliphatic and aromatic amines.

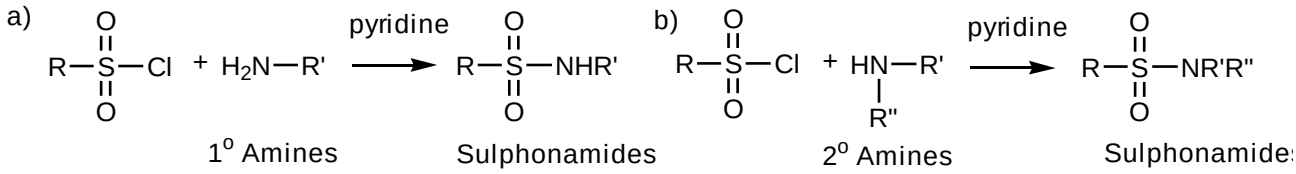


**Figure 23** Synthesis of sulphonamides.

## App 4.9 Synthesis of thioethers

Thioethers are prepared by the $S_N2$ nucleophilic substitution of primary or secondary alkyl halides with a thiolate anion ($RS^-$), which is generated by reacting a thiol with base (Fig. 24a). The reaction is similar to the Williamson ether synthesis. Symmetrical thioethers can be prepared by treating an alkyl halide with KOH and an equivalent of hydrogen sulphide. The reaction produces a thiol which is ionized again by KOH and reacts with another molecule of alkyl halide (Fig. 24b).

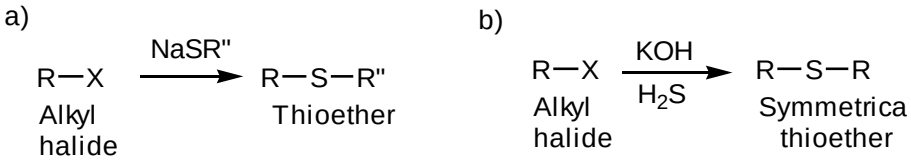


**Figure 24** Synthesis of thioethers from alkyl halides and thiols.

## App 4.10 Synthesis of ureas

Ureas can be synthesised from amines and isocyanates or alcohols and cyanamides.

### App 4.10.1 Reaction of an amine with an isocyanate

Ureas can be formed by reacting an amine with an isocyanate (Fig. 25). The amine acts as a nucleophile and adds to the central carbon of the isocyanate. Primary and secondary amines can be used for the reaction, as well as ammonia.

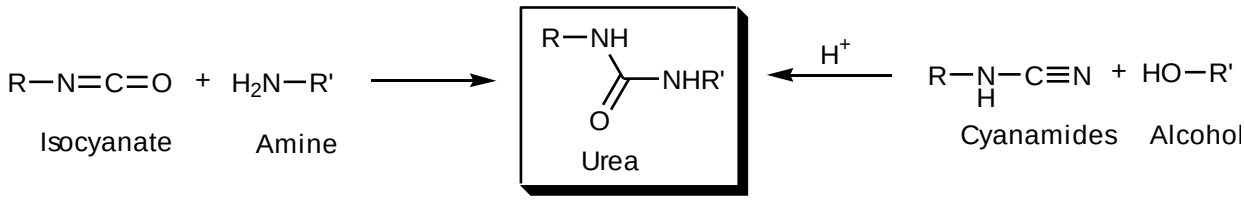


**Figure 25** Synthesis of ureas.

### App 4.10.2 Reaction of an alcohol with a cyanamide

The reaction of an alcohol with a cyanamide under strong acid conditions can also generate ureas (Fig. 25). The reaction involves protonation of the alcohol and loss of water to produce a cation, and so it works best for secondary, tertiary and benzylic alcohols as these generate stable carbocations.

**11. Synthesis of urethanes**

## App 4.11 Urethanes

Urethanes can be prepared from isocyanates or chloroformates.

### App 4.11.1 Reaction of an alcohol with an isocyanate

The reaction of an alcohol with an isocyanate generates a urethane (Fig. 26). The alcohol group acts as a nucleophile and adds to the carbon centre of the isocyanate.

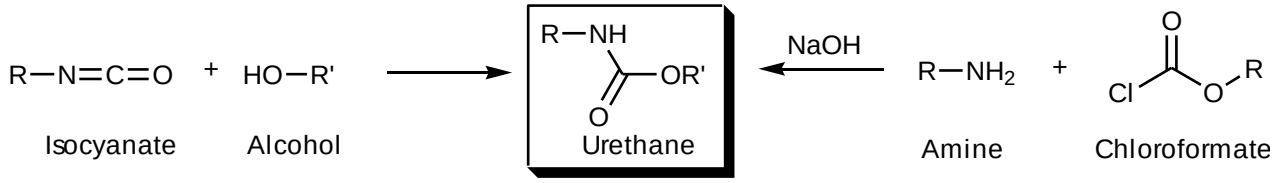


**Figure 26** Synthesis of urethanes.

### App 4.11.2 Reaction of an amine with a chloroformate

Treatment of an amine with a chloroformate also generates a urethane (Fig. 26). This reaction is frequently used to protect amine groups in peptide synthesis (Appendix 6.4). The chloroformate is added dropwise along with a solution of sodium hydroxide to a solution of the amine. The base is required to neutralise HCl which is formed during the reaction.

## App 4.12 Vinyl esters and ethers

Vinyl esters and ethers can be formed by treatment of an aldehyde with a base to generate an enolate ion. Alkylation or acylation of the enolate oxygen is then possible with highly reactive alkylating and

acylating agents such as chlorotrialkylsilanes, α-haloketones, alkyl tosylates and acid chlorides. The reaction works best in a polar, aprotic solvent such as HMPA, and the aldehyde must have an α-proton present to form the enolate (Fig. 27).

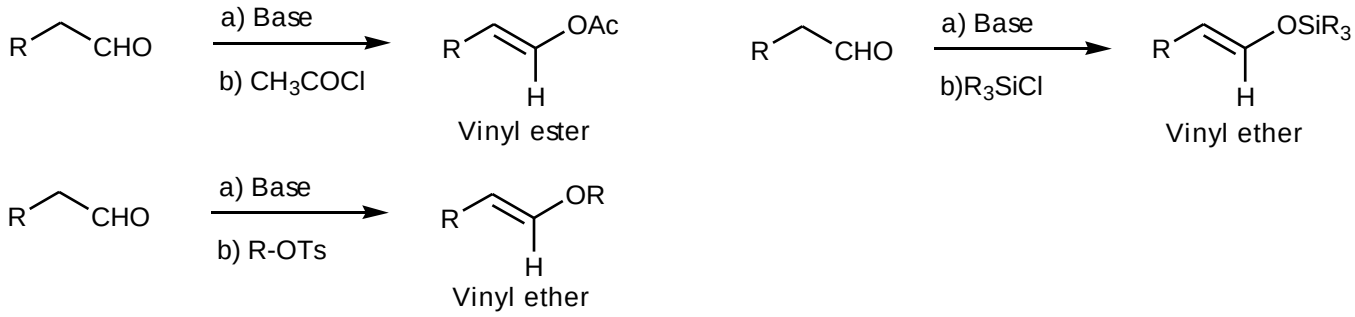


**Figure 27** Formation of vinyl esters and ethers.