Chapter 7

Nucleophilic aromatic substitution

In chapter 7 (section 7.3) we have seen the aromatic molecule acting as the nucleophile and attacking an electrophile. Electrophilic aromatic substitution is the most important mechanism for preparing aromatic drugs, and you may not study other mechanisms in your first year. However, you should be aware that there is more than one way to introduce a substituent into an aromatic ring, and we will now discuss some of the others.

We will now look at the reversed situation in which the aromatic molecule acts as an electrophile and reacts with a nucleophile; this is called Nucleophilic Aromatic Substitution (NAS or S_NAr). You should note two important points at the outset.

- Because NAS is quite different from EAS, the directing effects of substituents already on the ring are no longer relevant.
- NAS cannot increase the complexity of aromatic molecules because the simple substitution of hydrogen is not taking place; other groups are always required on the aromatic ring. This means that if a group can be introduced by EAS it probably will be.

There are three common mechanisms of NAS.

The addition-elimination mechanism

The "Addition-elimination" mechanism occurs in two steps. It requires both an electron withdrawing group, such as a nitro (NO_2) group, and a good leaving group, halogens work well. Additionally, the leaving group must be either *ortho*- or *-para*- to the electron withdrawing group. Figure 1 shows the mechanism of the reaction of sodium methoxide with 4-chloronitrobenzene; note how the electron withdrawing group acts as an electron sink (somewhere for the extra negative charge to go).

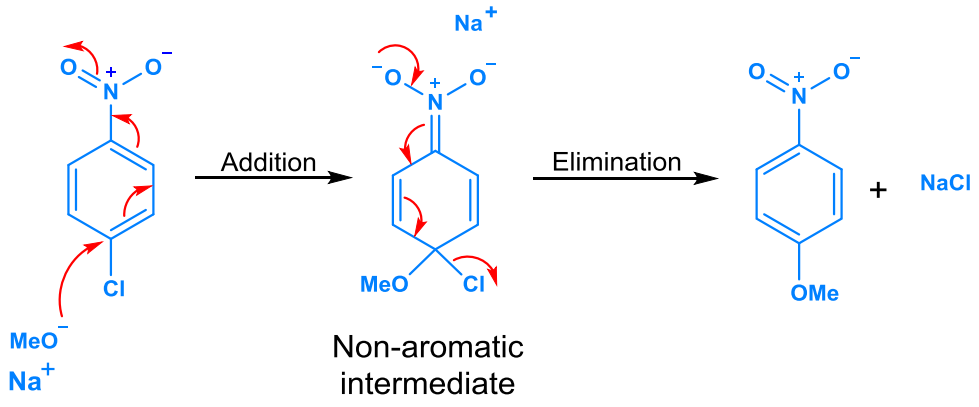

Figure 1: The addition-elimination mechanism of nucleophilic aromatic substitution.

The nucleophile, in this case sodium methoxide, attacks the aromatic ring at the carbon bearing the leaving group forming a non-aromatic intermediate. The intermediate can then re-aromatise by loss of the good leaving group. If the nucleophile is also a good leaving group, there is a problem – the wrong group may leave from the non-aromatic intermediate. This can be circumvented by using a large excess of the desired nucleophile but it is clearly better to plan your synthesis in such a way that this is not an issue. If we consider the *ortho*- and *meta*-isomers we can see that the *ortho*-isomer allows the electron withdrawing group to accept the charge but the *meta*-isomer cannot do this, so the reaction cannot and does not proceed, see Figure 2.

Make sure that you can convince yourself that the *ortho*- and *para*-isomers can accommodate the negative charge in the electron withdrawing group and that the *meta*-isomer cannot.

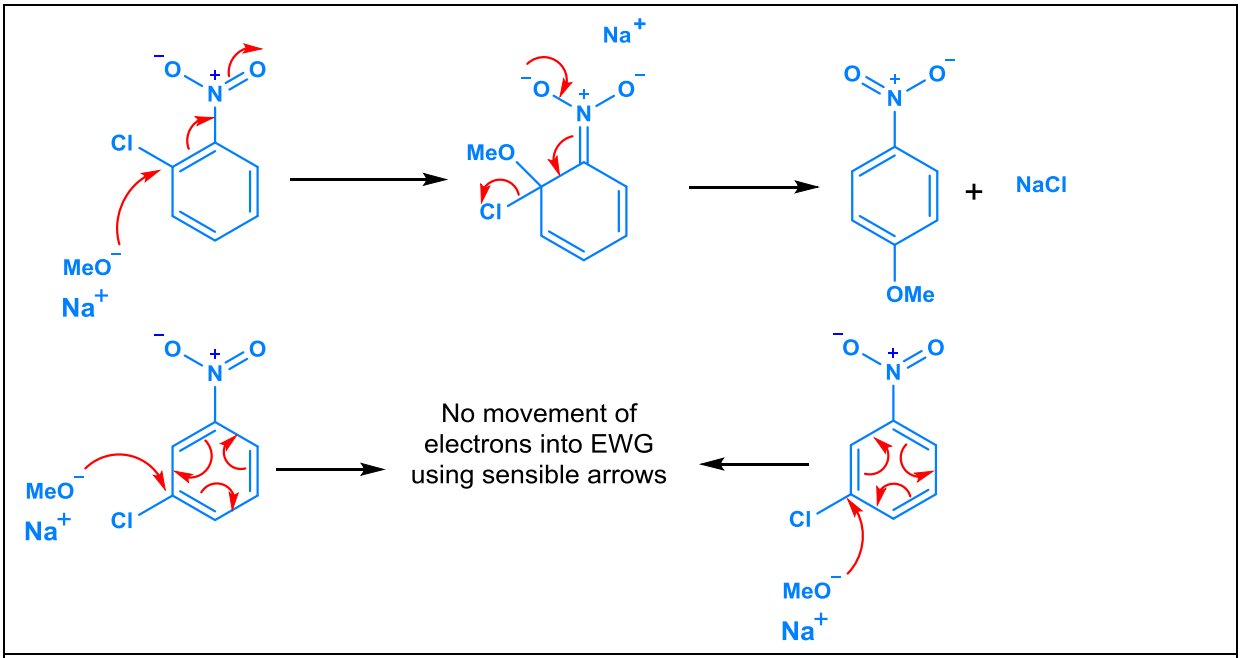

Figure 2: Attempted addition-elimination reactions for *ortho*- and *meta*-substitution.

The requirement for both functional groups is highlighted by the fact that this kind of reaction does not proceed if either chlorobenzene or nitrobenzene is employed in the place of *ortho*- or *para*-chloronitrobenzene. The overall transformation looks like an S_N2 reaction but it is important to note that such a mechanism is <u>impossible</u> on an aromatic halide!

The benzyne mechanism

The benzyne mechanism of nucleophilic aromatic substitution involves some unusual conditions and also an unusual intermediate, Figure 3 illustrates how this mechanism proceeds. The solvent, liquid ammonia, boils at -33ºC and cooling is required to keep the ammonia liquid and in the flask while the reaction is underway. Deprotonation by sodamide ($NaNH_2$) at the carbon adjacent to the carbon bearing the bromine forms an anion which can "kick out" the good leaving group, bromide, to form the odd looking benzyne (benzene with a triple bond). Sodamide can then attack the extremely reactive triple bond and the resultant carbon-based anion can remove a proton from ammonia to

regenerate sodamide. The use of strong base and unusual solvent mean that this is not very widely used but it can be useful. Note that in contrast to EAS reactions the aniline produced is essentially inert under the reaction conditions employed in this NAS reaction.

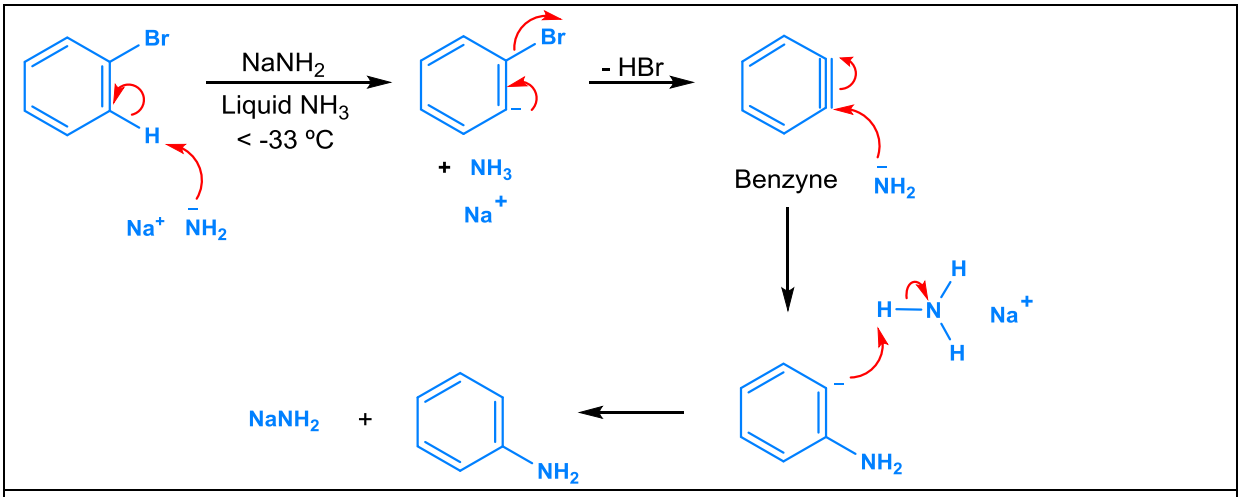

Figure 3: Conversion of bromobenzene to aniline via the benzyne mechanism.

Once again it might be tempting to consider that the mechanism of the reaction is S_N2 but remember it is impossible for aromatic halides to undergo an S_N2 reaction.

NAS Diazonium salts

This is a powerful methodology briefly mentioned on page 198 and in Figure 7.34 in which an amino group on an aromatic ring is converted to a diazonium salt which is, in turn, replaced by one of a number of nucleophiles. The term diazonium refers to the $-^{+}N{\equiv}N$ group, as illustrated in phenyldiazonium chloride shown in Figure 4. The exceptional leaving group ability (neutral, gaseous nitrogen is formed) of the diazonium group dictates its chemistry.

The reaction starts with the formation of NO^{+} from sodium nitrite and an acid, often HCl. This is an electrophilic reagent that reacts with the amine (note that the nitrogen of aniline takes the path of least resistance and reacts without breaking aromaticity) to ultimately form the diazonium salt. It is important to keep these salts at temperatures below about 5ºC otherwise they decompose via a S_N1 process with the loss of nitrogen gas to form the extremely reactive aromatic cation that will react rapidly with any nucleophile present such as water (from the reaction mixture) to form phenol. Once again it is important to reiterate that this is cannot be an S_N2 reaction!

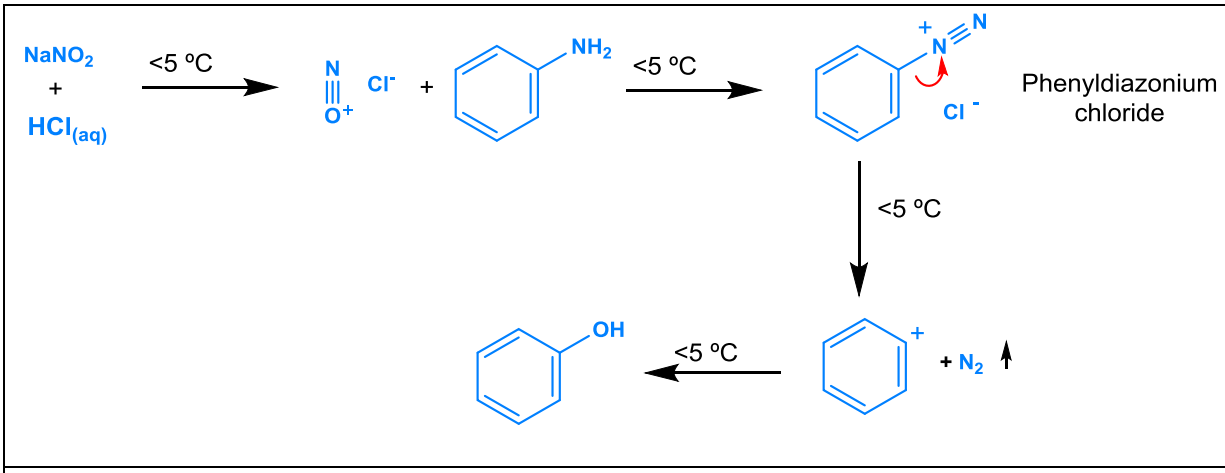

Figure 4: Conversion of aniline to phenol via an S_N1 mechanism.

Better nucleophiles than water can be employed to react with the aromatic diazonium salt, a selection are shown in Figure 5. Note that iodine and fluorine can be incorporated by this methodology and they can be difficult to install by other means.

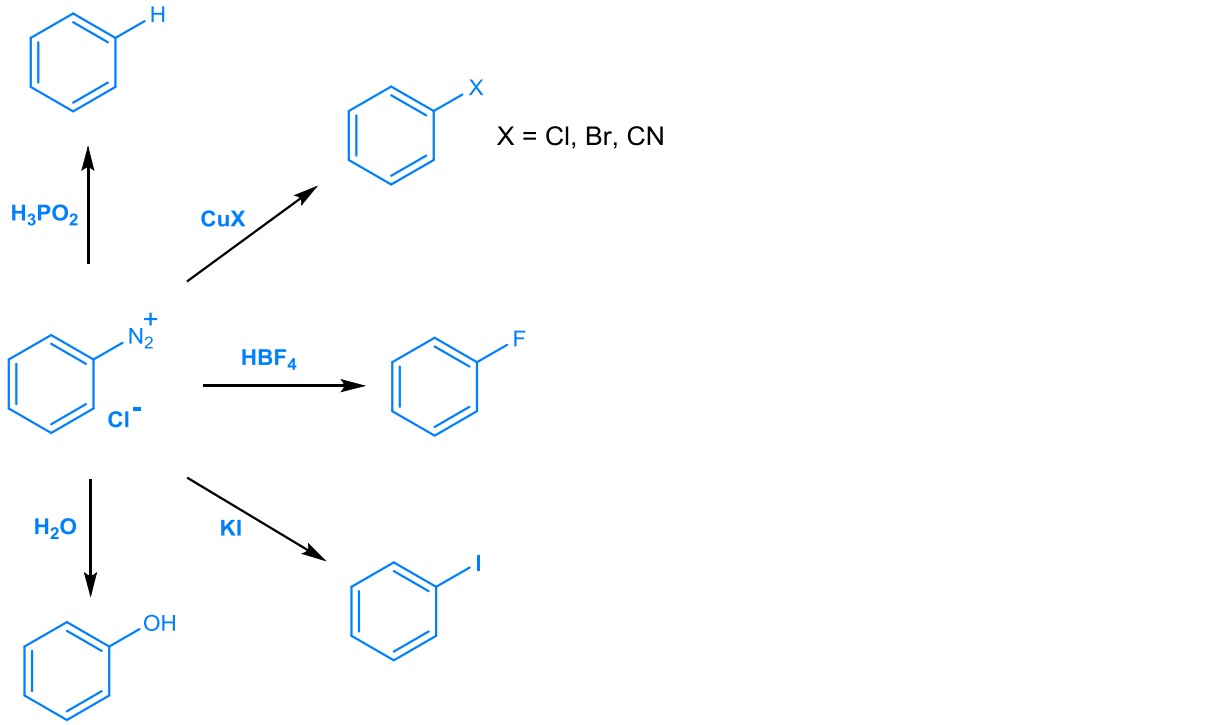

Figure 5: Reactions of phenyldiazonium chloride.

<CR> Radical chemistry Chapters 2 and 4 of this book

When targeting non-mammalian systems such as disease-causing bacteria or viruses it is sometime possible to exploit a non-mammalian enzyme or receptor system. Clearly this can offer benefits in

terms of side-effects if other off-target interactions can be avoided. **Bacterial DNA gyrase** offers just such a target and drugs that can disrupt its action have the potential to act as antibiotics. The Quinolone antibiotics operate by inhibiting bacterial DNA gyrase. The final steps of the synthesis ciprofloxacin are shown in Figure 6 and include two addition elimination reactions. You should notice that there are two good leaving groups (chloride) that are in either an *ortho*- or *para*-position with respect to the electron withdrawing group (the ketone). If two intermolecular reactions with two different nucleophiles were performed then we would expect that a mixture of isomers would be formed. However, the clever aspect of the synthesis of ciprofloxacin is that an intramolecular addition-elimination reaction is performed first by treatment with potassium carbonate (K_2CO_3). This permits the selective substitution of the *ortho*-chloride to form the 6-memebered ring shown in preference to substitution of the *para*-chloride which is too far away. Hydrolysis of the ethyl ester with aqueous acid forms the corresponding carboxylic acid. Finally, treatment with an excess of the second nucleophile, piperazine, substitutes the remaining chloride to form ciprofloxacin with complete isomeric control.

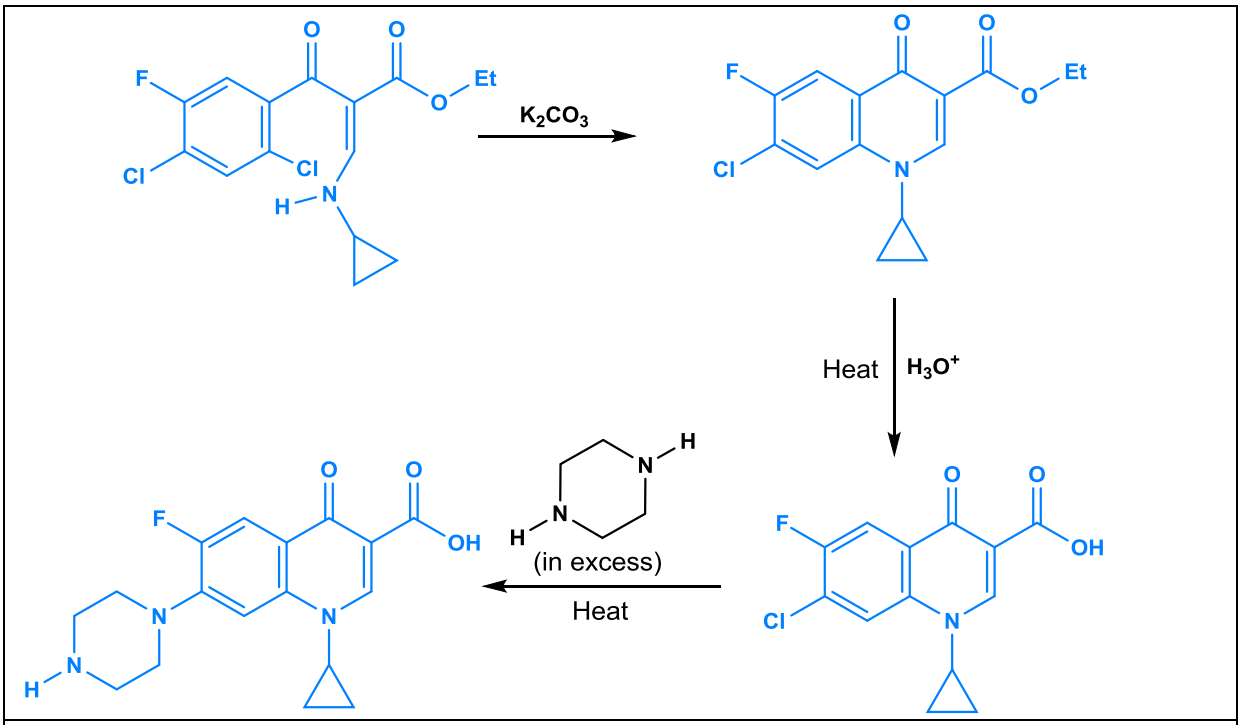

Figure 6: The final stages of the synthesis of ciprofloxacin.

Summary

NAS is a powerful methodology that complements the chemistry of EAS and can often be exploited to generate substitution patterns that are not readily accessible by EAS alone. It is often the case that combinations of EAS and NAS are employed to prepare compounds with interesting biological activity.