This is how the N-Boc pyrrole was made for use in the synthesis of epibatidine. The base used was the pyridine derivative DMAP, which you met earlier in the chapter. It has a $pK_{a\text{H}}$ of 9.7 and so produces small, equilibrating amounts of the anion as well as acting as a nucleophilic catalyst. ‘Boc anhydride’ is used as the acylating agent.

Anion formation is important in the next main section of this chapter, which is about what happens when we insert more nitrogen atoms into the pyrrole ring.

**Five-membered rings with two or more nitrogen atoms**

**Imidazole**

At the beginning of this chapter we imagined adding more nitrogen atoms to the pyrrole ring and noticed then that there were two compounds with two nitrogen atoms: pyrazole and imidazole.

Only one nitrogen atom in a five-membered ring can contribute two electrons to the aromatic sextet. The other replaces a CH group, has no hydrogen, and is like the nitrogen atom in pyridine. The black nitrogens are the pyrrole-like nitrogens; the green ones are pyridine-like. The lone pairs on the black nitrogens are delocalized round the ring; those on the green nitrogens are localized in $sp^2$ orbitals on nitrogen. We can expect these compounds to have properties intermediate between those of pyrrole and pyridine.

Imidazole is a stronger base than either pyrrole or pyridine—it has a $pK_{a\text{H}}$ of almost exactly 7, meaning that it is 50% protonated in neutral water. It is also more acidic than pyrrole, with a $pK_{a}$ of 14.5.

These curious results are a consequence of the 1,3 relationship between the two nitrogen atoms. Both the (protonated) cation and the (deprotonated) anion share the charge equally between the two nitrogen atoms—they are perfectly symmetrical and unusually stable.

Another way to look at the basicity of imidazole would be to say that both nitrogen atoms can act at once on the proton being attacked. It has to be the pyridine-like nitrogen that actually captures the proton but the pyrrole nitrogen can help by using its delocalized electrons like this.

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**Anions of pyrroles react with electrophiles at the nitrogen atom.**

DMAP’s $pK_{a\text{H}}$ of 9.7 is between those of pyridine (5.5) and tertiary alkyl amines (ca. 10) but much closer to the latter.

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A similar effect accounts for the basicity of DBU and DBN: see p. 000.
Nature makes use of this property by having imidazole groups attached to proteins in the form of the amino acid histidine and using them as nucleophilic, basic and acidic catalytic groups in enzyme reactions (this will be discussed in Chapters 49 and 50). We use this property in the same way when we add a silyl group to an alcohol. Imidazole is a popular catalyst for these reactions.

A weakly basic catalyst is needed here because we want to discriminate between the primary and secondary alcohols in the diol. Imidazole is too weak ($pK_{aH} \approx 7$) to remove protons from an alcohol ($pK_a \approx 16$) but it can remove a proton after the OH group has attacked the silicon atom.

In fact, the imidazole is also a nucleophilic catalyst of this reaction, and the first step is substitution of Cl by imidazole—that is why the leaving group in the last scheme was shown as 'X'. The reaction starts off like this.

The same idea leads to the use of Carbonyl Diimidazole (CDI) as a double electrophile when we want to link two nucleophiles together by a carbonyl group. Phosgene ($COCl_2$) has been used for this but it is appallingly toxic (it was used in the First World War as a poison gas with dreadful effects). CDI is safer and more controlled. In these reactions imidazole acts (twice) as a leaving group.

The amino group probably attacks first to displace one imidazole anion, which returns to deprotonate the ammonium salt. The alcohol can then attack intramolecularly displacing the second imidazole anion, which deprotonates the OH group in its turn. The other product is just two molecules of imidazole.
The relationship between the delocalized imidazole anion and imidazole itself is rather like that between an enolate anion and an enol. It will come as no surprise that imidazole tautomerizes rapidly at room temperature in solution. For the parent compound the two tautomers are the same, but with unsymmetrical imidazoles the tautomerism is more interesting. We will explore this question alongside electrophilic aromatic substitution of imidazoles.

Imidazoles with a substituent between the two nitrogen atoms (position 2) can be nitrated with the usual reagents and the product consists of a mixture of tautomers.

The initial nitration may occur at either of the remaining sites on the ring with the electrons coming from the pyrrole-like nitrogen atom. Tautomerism after nitration gives the mixture.

The tautomerism can be stopped by alkylation at one of the nitrogen atoms. If this is done in basic solution, the anion is an intermediate and the alkyl group adds to the nitrogen atom next to the nitro group. Again, it does not matter from which tautomer the anion is derived—there is only one anion delocalized over both nitrogen atoms and the nitro group. One reason for the formation of this isomer is that it has the linear conjugated system between the pyrrole-like nitrogen and the nitro group (see p. 000).

Important medicinal compounds are made in this way. The antiparasitic metronidazole comes from 2-methyl imidazole by nitration and alkylation with an epoxide in base.

The triazoles

There are two triazoles, and each has one pyrrole-like nitrogen and two pyridine-like nitrogens. Both triazoles have the possibility of tautomerism (in 1,2,3-triazole the tautomers are identical) and both give rise to a single anion.
The 1,2,4-triazole is more important because it is the basis of the best modern agricultural fungicides as well as drugs for fungal diseases in humans. The extra nitrogen atom makes it more like pyridine and so more weakly basic, but it increases its acidity so that the anion is now easy to make.

The fungicides are usually made by the addition of the triazole anion to an epoxide or other carbon electrophile. The anion normally reacts at one of the two linked nitrogen atoms (it does not matter which—the product is the same).

A modern example of an agent used against human fungal infections is Pfizer’s fluconazole, which actually contains two triazoles. The first is added as the anion to an $\alpha$-chloroketone and the second is added to an epoxide made with sulfur ylid chemistry (you will meet this in Chapter 46). Note that weak bases were used to catalyse both of these reactions. Triazole is acidic enough for even NaHCO$_3$ to produce a small amount of the anion.

Tetrazole

There is only one isomer of tetrazole or of substituted tetrazoles, as there is only one carbon atom in the ring, though there are two tautomers. The main interest in tetrazoles is that they are rather acidic: the $pK_a$ for the loss of the NH proton to form an anion is about 5, essentially the same as that of a carboxylic acid. The anion is delocalized over all four nitrogen atoms (as well as the one carbon atom), and four nitrogen atoms do the work of two oxygen atoms.
Because tetrazoles have similar acidities to those of carboxylic acids, they have been used in drugs as replacements for the CO\(_2\)H unit when the carboxylic acid has unsatisfactory properties for human medicine. A simple example is the anti-arthritis drug indomethacin whose carboxylic acid group may be replaced by a tetrazole with no loss of activity.

**Benzo-fused heterocycles**

**Indoles are benzo-fused pyrroles**

Indomethacin and its tetrazole analogue contain pyrrole rings with benzene rings fused to the side. Such bicyclic heterocyclic structures are called *indoles* and are our next topic. Indole itself has a benzene ring and a pyrrole ring sharing one double bond, or, if you prefer to look at it this way, it is an aromatic system with 10 electrons—eight from four double bonds and the lone pair from the nitrogen atom.

Indole is an important heterocyclic system because it is built into proteins in the form of the amino acid tryptophan (Chapter 49), because it is the basis of important drugs such as indomethacin, and because it provides the skeleton of the *indole alkaloids*—biologically active compounds from plants including strychnine and LSD (alkaloids are discussed in Chapter 51).

**Nitrogen atoms and explosions**

Compounds with even two or three nitrogen atoms joined together, such as diazomethane (CH\(_2\)N\(_2\)) or azides (RN\(_3\)), are potentially explosive because they can suddenly give off stable gaseous nitrogen. Compounds with more nitrogen atoms, such as tetrazoles, are likely to be more dangerous and few people have attempted to prepare pentazoles. The limit is reached with diazotetrazole, with the amazing formula CN\(_6\). It is made by diazotization of 5-aminotetrazole, which first gives a diazonium salt.

The diazonium salt is extremely dangerous: ‘It should be emphasised that [the diazonium salt] is extremely explosive and should be handled with great care. We recommend that no more than 0.75 mmol be isolated at one time. Ethereal solutions are somewhat more stable but explosions have occurred after standing at \(-70\) °C for 1 hr.’ So much for that, but what about the diazo compound? It is extremely unstable and decomposes to a carbene with loss of one molecule of nitrogen and then loses two more to give...

All that is left is a carbon atom and this is one of very few ways to make carbon atoms chemically. The carbon atoms have remarkable reactions and these have been briefly studied, but the hazardous preparation of the starting materials discourages too much research. However, you will see in the next chapter that 1-aminotetrazole is a useful starting material for making an anti-allergic drug.