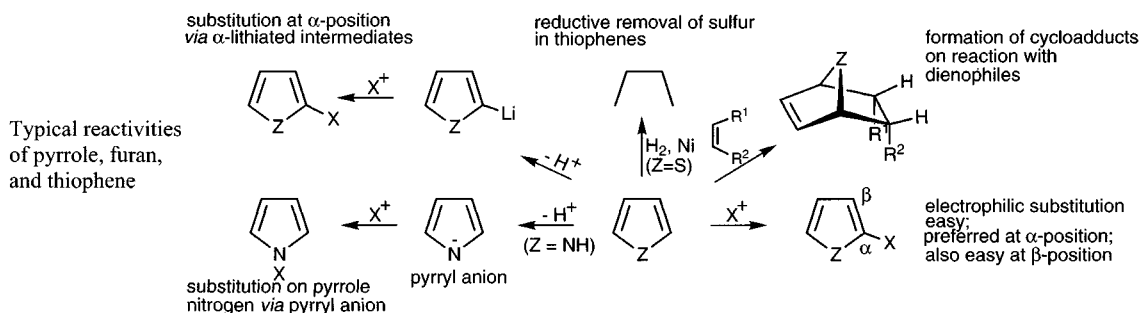
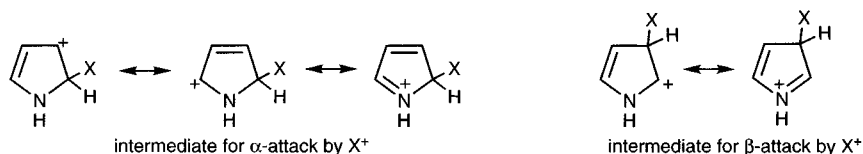


12 Typical reactivity of pyrroles, thiophenes, and furans

In this chapter are gathered the most important generalisations which can be made, and the general lessons which can be learned about the reactivity, and relative reactivities, one with the other, of the prototypical five-membered aromatic heterocycles: pyrroles, thiophenes and furans.

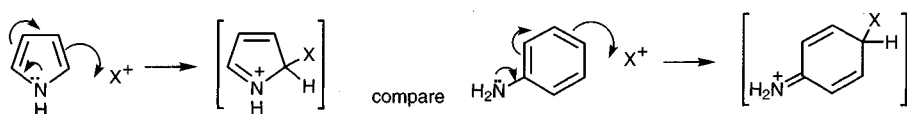


The chemistry of pyrrole, thiophene and furan is dominated by a readiness to undergo electrophilic substitution, preferentially at an α -position but, with only slightly less alacrity, also at a β -position, should the α positions be blocked. For the beginning student of heterocyclic chemistry it is worth re-emphasising the stark contrast between the five- and six-membered heterocycles – the former react much more readily with electrophiles than does benzene and the latter much less readily.

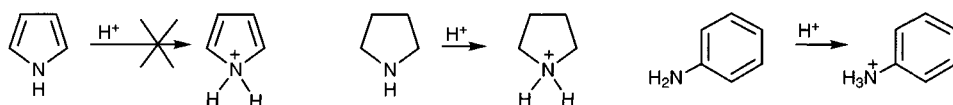


Positional selectivity in these five-membered systems, indeed their high reactivity to electrophilic attack, are well explained by a consideration of the Wheland intermediates (and by implication, the transition states which lead to them) for electrophilic substitution. Intermediate cations from both α - and β -attack are stabilised (shown for attack on pyrrole). The delocalisation, involving donation of electron density from the hetero atom, is greater in the intermediate from α -attack, as illustrated by the number of low energy resonance contributors which can be drawn. Note that the C–C double bond in the intermediate for β -attack is not, and cannot become involved in delocalisation of the charge.

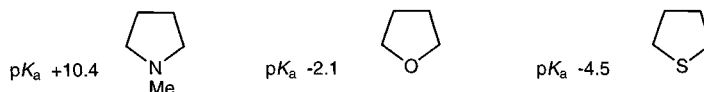
There is a simple parallelism between the reaction of a pyrrole with an electrophile and the comparable reaction of an aniline, and indeed pyrrole is in the same range of reactivity towards electrophiles as is aniline.



The five-membered heterocycles do not react with electrophiles at the hetero atom; perhaps this surprises the heterocyclic newcomer most obviously with respect to pyrrole, for here, it might have been anticipated, the nitrogen lone pair would be easily donated to an incoming electrophile, as it certainly would be in reactions of its saturated counterpart, pyrrolidine. The difference is that in pyrrole, electrophilic addition at the nitrogen would lead to a substantial loss of resonance stabilisation – the molecule would be converted into a cyclic butadiene, with an attached nitrogen carrying a positive charge localised on that nitrogen atom. The analogy with aniline falls down for, of course, anilines do react easily with simple electrophiles (e.g. protons) at nitrogen. The key difference is that, although some stabilisation in terms of overlap between the aniline nitrogen lone pair and benzenoid π -system is lost, the majority of the stabilisation energy, associated with the six-electron aromatic π -system, is retained when aniline nitrogen donates its lone pair of electrons to a proton (electrophile).

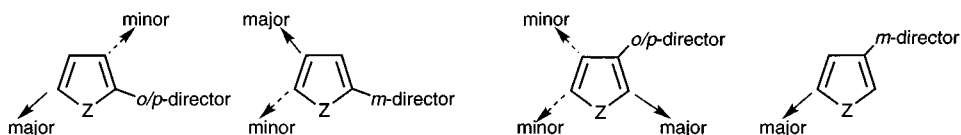


Of the trio – pyrrole, furan and thiophene – the first is by far the most susceptible to electrophilic attack: this susceptibility is linked to the greater electron-releasing ability of neutral trivalent nitrogen, and the concomitant greater stability of a positive charge on tetravalent nitrogen. This finds its simplest expression in the relative basicities of saturated amines, sulfides and ethers, respectively, which are seen to parallel nicely the relative order of reactivity of pyrrole, furan and thiophene towards electrophilic attack at carbon, but involving major assistance by donation from the hetero atom, i.e. the development of positive charge on the hetero atom.



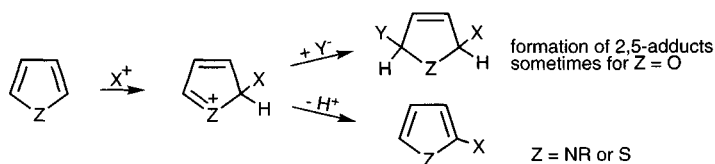
In qualitative terms, the much greater reactivity of pyrrole is illustrated by its rapid reaction with weak electrophiles like benzenediazonium cation and nitrous acid, neither of which react with furan or thiophene. It is relevant to note that *N,N*-dimethylaniline reacts rapidly with these reactants, where anisole does not.

Substituents ranged on five-membered rings have directing effects comparable to those which they exert on a benzene ring. Alkyl groups, for example, direct *ortho* and *para*, and nitro groups direct *meta* although, strictly, these two terms cannot be applied to the five-membered situation. The very strong tendency for α electrophilic substitution is however the dominating influence in most instances, and products resulting from attack following guidance from the substituent are generally minor products in mixtures where the dominant substitution is at an available α -position. The influence of substituents is felt least in furans.



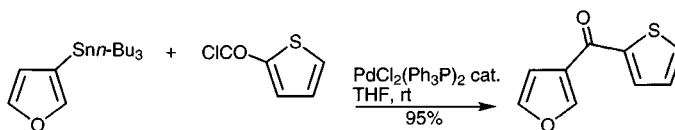
An aspect of the chemistry of furans is the occurrence of a number of 2,5-additions initiated by electrophilic attack: a Wheland intermediate is formed normally but then

adds a nucleophile, when a sufficiently reactive one is present, instead of then losing a proton. Conditions can, however, usually be chosen to allow the formation of a 'normal' α -substitution product if desired. The occurrence of such processes in the case of furan is generally considered to be associated with its lower aromatic resonance stabilisation energy – there is less to regain by loss of a proton and the consequent return to an aromatic furan.



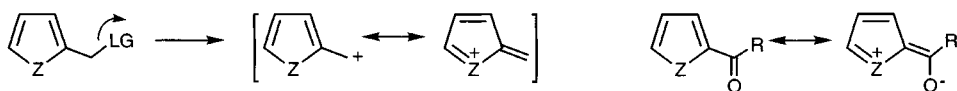
The lower aromaticity of furans also manifests itself in a much greater tendency to undergo cycloadditions, as a 4- π , diene component in Diels-Alder reactions. That is to say, furans are much more like dienes, and less like a six-electron aromatic system, than are pyrroles and thiophenes. However, the last two systems can be made to undergo cycloadditions by increasing the pressure or, in the case of pyrroles, by 'reducing the aromaticity' by the device of inserting an electron-withdrawing group onto the nitrogen.

In direct contrast with electron-deficient heterocycles like pyridines and the diazines, the five-membered systems do not undergo nucleophilic substitutions, except in situations (especially in furan and thiophene chemistry) where halide is situated *ortho* or *para* to a nitro group. In the manipulation of the five-membered heterocycles of this group, extensive use has been made of the various palladium(0)-catalysed couplings available, as illustrated below (see section 2.7 for a detailed discussion).



Deprotonations are extremely important: furan and thiophene are deprotonated by strong bases, such as *n*-butyllithium or lithium diisopropylamide, at their α -positions, because here the heteroatom can exert its greatest acidifying influence by inductive withdrawal of electrons, to give anions which can then be made to react with the whole range of electrophiles affording α -substituted furans and thiophenes. This methodology compliments the use of electrophilic substitutions to introduce groups, also regioselectively α , but has the advantage that even weak electrophiles can be utilised. The employment of metallated *N*-substituted (blocked) pyrroles is an equally valid strategy for producing α -substituted pyrroles. Pyrroles which have an *N*-hydrogen are deprotonated at the nitrogen, and the pyrrol anion thus generated is nucleophilic at the hetero atom, providing a means for the introduction of electrophilic groups on nitrogen.

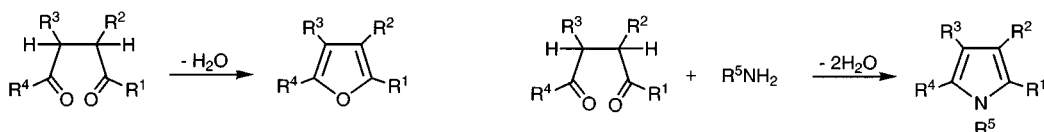
The potential for interaction of the hetero atom (electron donation) with positive charge on a side-chain, especially at an α -position, has a number of effects: amongst the most important is the enhanced reactivity of side-chain derivatives carrying leaving groups.



Similarly, carbonyl groups attached to five-membered heterocycles have somewhat reduced reactivity, as implied by the resonance contributor shown.

Generally speaking, the five-membered heterocycles are far less stable to oxidative conditions than benzenoid aromatic substances, with thiophenes bearing the closest similarity – in many ways thiophenes, of the trio, are the most like carboaromatic compounds. Hydrogenation of thiophenes, particularly over nickel as catalyst, leads to saturation and removal of the hetero atom. Some controlled chemical reductions of pyrroles and furans are known, which give dihydro-products.

The ring synthesis of five-membered heterocycles has been investigated extensively and many and subtle methods have been devised. Each system can be prepared from 1,4-dicarbonyl compounds, for furans by acid catalysed cyclising dehydration, and for pyrroles and thiophenes by interaction with ammonia or primary amine, or a source of sulfur, respectively.



As illustrations of the variety of methods available, the three processes below show (i) the addition of isonitrile anions to α,β -unsaturated nitro compounds, with loss of nitrous acid to aromatise, (ii) the interaction of thioglycolates with 1,3-dicarbonyl compounds, for the synthesis of thiophene-2-esters, and (iii) the cycloaddition/cycloreversion preparation of furans from oxazoles.

