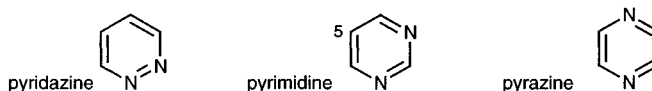
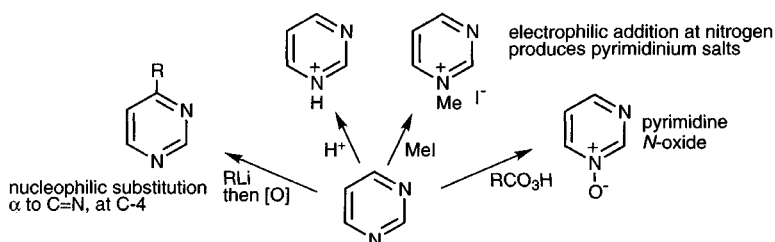


10 Typical reactivity of the diazines: pyridazine, pyrimidine and pyrazine



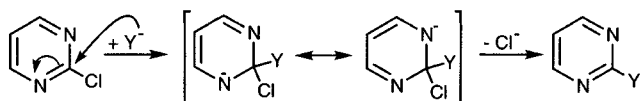
The diazines – pyridazine, pyrimidine and pyrazine – contain two imine nitrogen atoms, so the lessons learnt with regard to pyridine (chapter 5) are, in these heterocycles, exaggerated. Two heteroatoms withdraw electron density from the ring carbons even more than in pyridine, so the unsubstituted diazines are even more resistant to electrophilic substitution than is pyridine. A corollary of course, developed below, is that this same increased electron deficiency at carbon makes the diazines more easily attacked by nucleophiles than pyridines. The availability of nitrogen lone pair(s) is also reduced: each of the diazines is appreciably less basic than pyridine, reflecting the destabilising influence of the second nitrogen on the *N*-protonation. Nevertheless, diazines will form salts and will react with alkyl halides and with peracids to give *N*-alkyl quaternary salts and *N*-oxides, respectively. Generally speaking, such electrophilic additions take place at one nitrogen only, because the presence of the positive charge in the products renders the second nitrogen extremely unreactive towards a second electrophilic addition.

Typical reactivity of diazines exemplified by pyrimidine



A very characteristic feature of the chemistry of diazines, which is associated with their strongly electron-poor nature, is that they add nucleophilic reagents easily. Without halide to be displaced, such adducts require an oxidation to complete an overall substitution. However, halo-diazines, where the halide is α or γ to a nitrogen, undergo very easy nucleophilic displacements, the intermediates being particularly well stabilised.

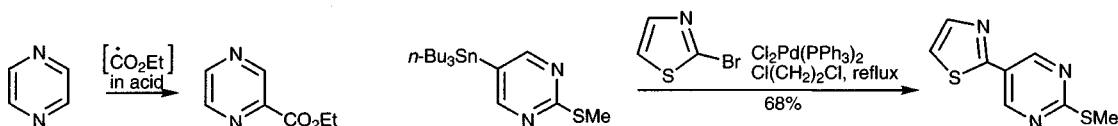
All positions on each of the diazines, with the sole exception of the 5-position of a pyrimidine, are α and/or γ to an imine ring nitrogen and, in considering nucleophilic addition/substitution, it must be remembered that there is also an additional nitrogen withdrawing electron density. As a consequence, all the monohalodiazines are more reactive than either 2- or 4-halopyridines. The 2- and 4-halopyrimidines are particularly reactive because the anionic intermediates (shown below for attack on 2-chloropyrimidine) derive direct mesomeric stabilisation from both nitrogen atoms.



Despite this particularly strong propensity for nucleophilic addition, C-lithiation of diazines can be achieved by either metal-halogen exchange or, by deprotonation *ortho* to chloro or alkoxy substituents, though very low temperatures must be utilised in order to avoid nucleophilic addition of the reagent.

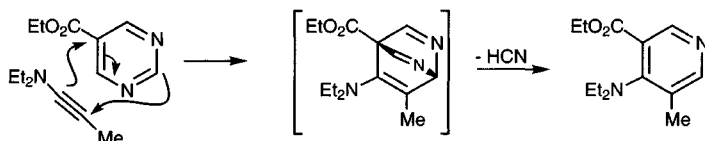


In line with their susceptibility to nucleophilic addition, diazines also undergo Minisci radical substitution with ease. Considerable use has been made in diazine chemistry of palladium(0)-catalysed coupling processes, one of which is illustrated below (see section 2.7 for a detailed discussion).

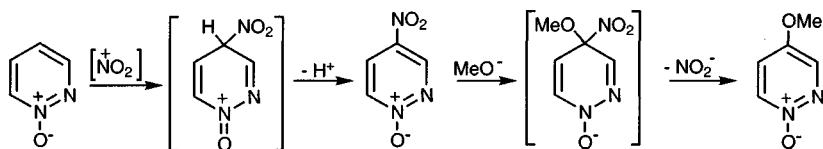


Further examples of the enhancement of those facets of pyridine chemistry associated with the imine electron withdrawal, include a general stability towards oxidative degradation but, on the other hand, a tendency to undergo rather easy reduction of the ring.

Although there is always debate about quantitative measures of aromaticity, it is agreed that the diazines are less resonance stabilised than pyridines – they are ‘less aromatic’. Thus, Diels-Alder additions are known for all three systems, with the heterocycle acting as a diene; initial adducts lose a small molecule – hydrogen cyanide in the pyrimidine example shown – to afford a final stable product.

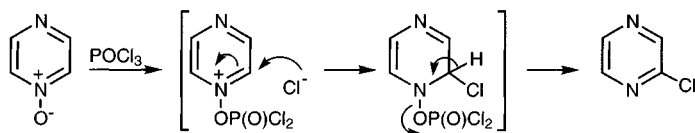


N-Oxides, just as in the pyridine series, show a remarkable duality of effect – they encourage both electrophilic substitutions and nucleophilic displacements. The sequence below shows pyridazine *N*-oxide undergoing first, electrophilic nitration, then, the product, nucleophilic displacement, with nitrite as leaving group.

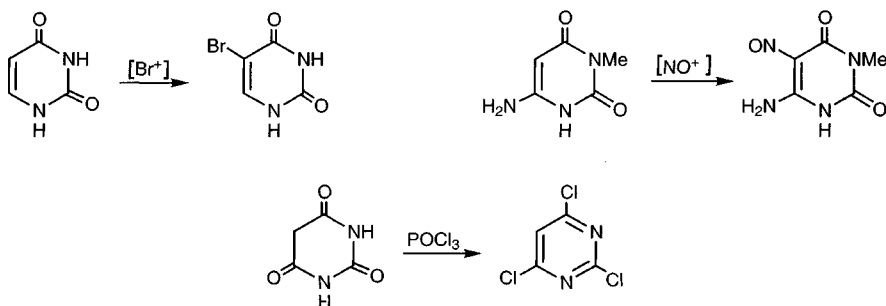


N-Oxide chemistry in six-membered heterocycles provides considerable scope for synthetic manipulations. One of the very useful transformations is the introduction of halide α to a nitrogen on reaction with phosphorus or sulfur halides, the conversion being initiated by oxygen attack on the phosphorus (sulfur). The power of

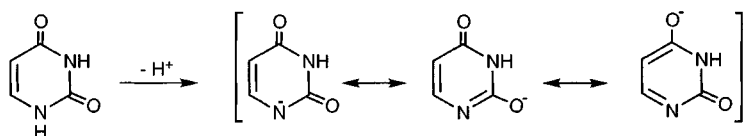
this transformation can be emphasised by noting that the unsubstituted heterocycle is converted, in the two steps, into a halide with its potential for subsequent displacement by nucleophiles.



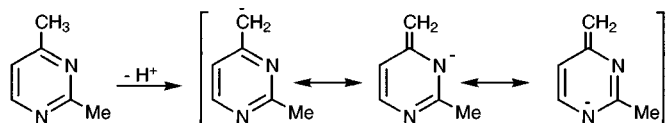
The most studied diazine derivatives are the oxy- and amino-pyrimidines since uracil, thymine, and cytosine are found as bases in DNA and RNA. It is the enamide-like character of the double bonds in diazines with two oxygen substituents which allows electrophilic substitution – uracil, for example, can be brominated. One amino substituent permits electrophilic ring substitution and two amino, or one amino and one oxy, substituent, permit reaction with even weakly electrophilic reactants.



Diazinones, like pyridones, react with phosphorus halides with overall conversion into halides. Anions produced by *N*-deprotonation of diazinones are ambident, with a phenolate-like resonance contributor, but they generally react with electrophilic alkylating agents at nitrogen, rather than oxygen.

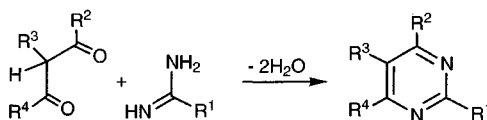
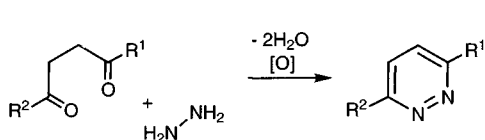


Diazine alkyl groups, with the exception of those at the 5-position of pyrimidine, can undergo condensation reactions which utilise the carbanion produced by removal of a proton. As in pyridine chemistry, formation of these anions is made possible by delocalisation of the charge onto one (or more) of the ring nitrogen atoms.



As can be seen from the illustrations below, each of the diazines can be constructed from an appropriate source of two nitrogens and a dicarbonyl compound. In the case of pyridazines, the nitrogen source is of course hydrazine and this in combination with 1,4-dicarbonyl compounds readily produces dihydropyridazines which are very easily dehydrogenated. Pyrimidines result from the interaction of a 1,3-dicarbonyl component and an amidine (as shown) or a urea (when 2-pyrimidones are formed) or

a guanidine (when 2-aminopyrimidines are formed), without the requirement for an oxidation step.



To access a pyrazine in this way one needs a 1,2-diamine and a 1,2-dicarbonyl compound, and a subsequent oxidation, but if neither component is symmetrical, mixtures are formed. The dimerisation of 2-aminocarbonyl compounds also generates symmetrically substituted dihydropyrazines – perhaps the best known examples of such dimerisations involve the natural amino acids and their esters which dimerise to give dihydropyrazine-2,5-diones – ‘diketopiperazines’.

