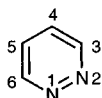
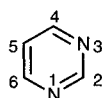


# 11 The diazines: pyridazine, pyrimidine, and pyrazine: reactions and synthesis

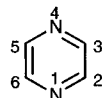
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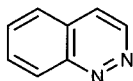
pyridazine



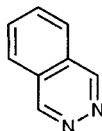
pyrimidine



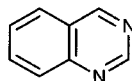
pyrazine



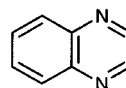
cinnoline



phthalazine



quinazoline

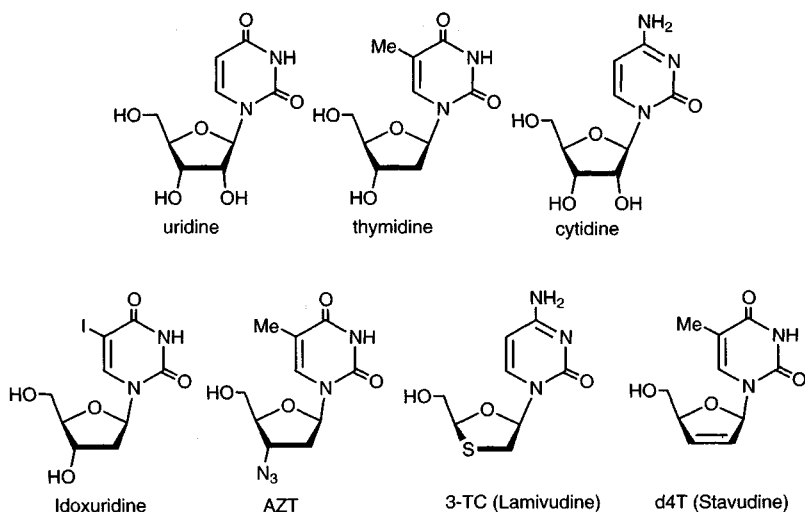


quinoxaline

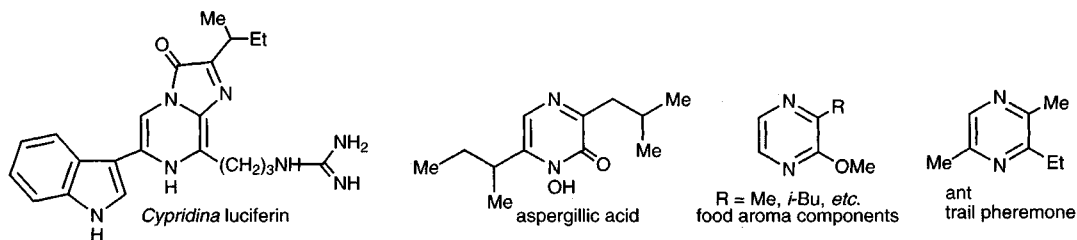
The three diazines, pyridazine,<sup>1</sup> pyrimidine,<sup>2</sup> and pyrazine<sup>3</sup> are stable, colourless compounds which are soluble in water. The three parent heterocycles, unlike pyridine, are expensive and not readily available and so are seldom used as starting materials for the synthesis of their derivatives. There are only four ways in which a benzene ring can be fused to a diazine: cinnoline, phthalazine, quinazoline and quinoxaline are the bicyclic systems thus generated.

One striking aspect of the physical properties of the diazine trio is the high boiling point of pyridazine (207 °C), 80–90 °C higher than that of pyrimidine (123 °C), pyrazine (118 °C), or indeed other azines, including 1,3,5-triazine, all of which also boil in the range 114–124 °C. The high boiling point of pyridazine is attributed to the polarisability of the N–N unit which results in extensive dipolar association in the liquid.

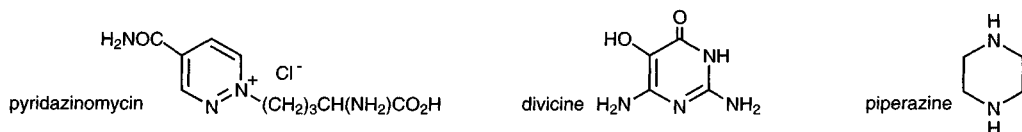
The most important naturally occurring diazines are the pyrimidine bases uracil, thymine and cytosine, which are constituents of the nucleic acids.<sup>4</sup> Following from this, several pyrimidine nucleoside analogues have been developed as anti-viral agents, for example Idoxuridine is used in the treatment of *Herpes* infections of the eye, and AZT is the most widely used anti-AIDS drug; 3-TC (Lamivudine) is used to treat both hepatitis B and AIDS, and d4T (Stavudine) is a fourth drug approved for treatment of HIV infection and AIDS. The pyrimidine ring also occurs in the vitamin thiamin (section 21.11). The nucleic acid pyrimidines are often drawn horizontally transposed from the representations used in this chapter, i.e. with N-3 to the 'North-West', mainly to draw attention to their structural similarity to the pyrimidine ring of the nucleic acid purines (chapter 24), which are traditionally drawn with the pyrimidine ring on the left.



The pyrazine ring system is found in the fungal metabolite aspergillic acid and in dihydro-form in the luciferins of several beetles, including the firefly, *Cypridina hilgendorffii*, and is responsible for the chemiluminescence<sup>5</sup> of this ostracod. Quite simple methoxypyrazines are very important components of the aromas of many fruits and vegetables, such as peas and Capsicum peppers, and also of wines.<sup>6</sup> Although present in very small amounts, they are extremely odorous and can be detected at concentrations as low as 0.00001 ppm. Related compounds, probably formed by the pyrolysis of amino acids during the process of cooking, are also important in the aroma of roasted meats. Several polyalkylpyrazines are insect pheromones, for example 2-ethyl-3,6-dimethylpyrazine is the major component of the trail pheromone of the South American leaf-cutting ant.

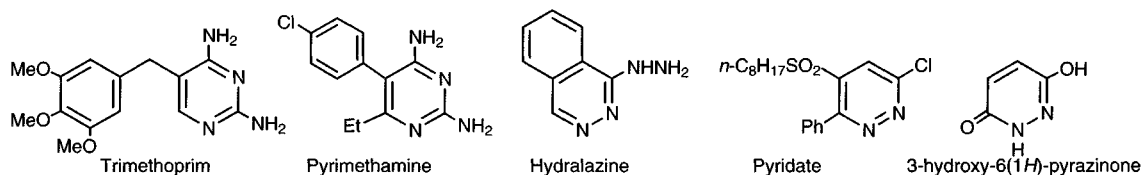


There are relatively few naturally occurring pyridazines, for example some fungal metabolites from *Streptomyces* species, consisting mainly of reduced systems, and the quaternary salt pyridazinomycin. Divicine, present as a glucoside in broad beans and related plants, is the toxic agent responsible for 'favism', a serious hemolytic reaction in genetically susceptible people (of Mediterranean origin). Piperazine (hexahydropyrazine) is used in the treatment of intestinal nematode (worm) infections.



Derivatives of all three heterocyclic systems have been widely investigated for use in synthetic drugs (see also above); amongst the most commonly used compounds are

the antibacterial Trimethoprim, the antimalarial Pyrimethamine and the anti-hypertensive agent Hydralazine (containing a phthalazine nucleus).



A number of pyridazines are important as selective plant growth regulators and are used as herbicides, e.g. Pyridate; 3-hydroxy-6(1*H*)-pyrazinone, is used as a lawn weedkiller.

## 11.1 Reactions with electrophilic reagents

### 11.1.1 Addition at nitrogen<sup>7</sup>

#### 11.1.1.1 Protonation

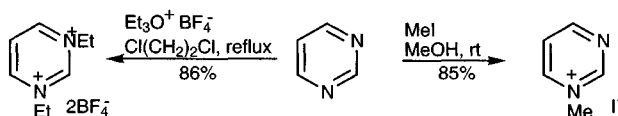
The diazines, pyridazine ( $pK_a$  2.3), pyrimidine (1.3), and pyrazine (0.65) are essentially monobasic substances, and considerably weaker, as bases, than pyridine (5.2). This reduction in basicity is believed to be largely a consequence of destabilisation of the mono-protonated cations due to inductive withdrawal by the second nitrogen atom. Secondary effects, however, determine the order of basicity for the three systems: lone pair repulsion between the two adjacent nitrogen atoms in pyridazine means that protonation occurs more readily than if inductive effects, only, were operating. In the case of pyrazine, mesomeric interaction between the protonated and neutral nitrogen atoms probably destabilises the cation.

*N,N'*-Diprotonation is very much more difficult and has only been observed in very strongly acidic media. Of the trio, pyridazine ( $pK_{a(2)} -7.1$ ) is the most difficult from which to generate a dication, probably due to the high energy associated with the juxtaposition of two immediately adjacent positively charged atoms, but pyrimidine ( $pK_{a(2)} -6.3$ ) and pyrazine ( $pK_{a(2)} -6.6$ ) are only marginally easier to doubly protonate.

Substituents can affect basicity (and nucleophilicity) both inductively and mesomerically, but care is needed in the interpretation of  $pK_a$  changes, for example it is important to be sure which of the two nitrogens of the substituted azine is protonated (see also section 11.1.1.2).

#### 11.1.1.2 Alkylation

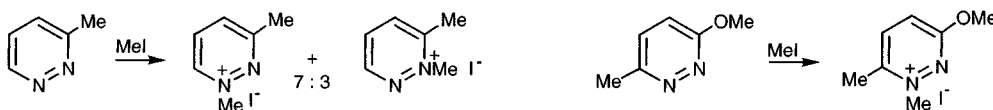
The diazines react with alkyl halides to give mono-quaternary salts, though somewhat less readily than comparable pyridines. Dialkylation cannot be achieved with simple alkyl halides, however the very much more reactive trialkyloxonium tetrafluoroborates do convert all three systems into di-quaternary salts.<sup>8</sup>



Pyridazine is the most reactive in alkylation reactions and this again has its origin in the lone pair/lone pair interaction between the nitrogen atoms. This phenomenon

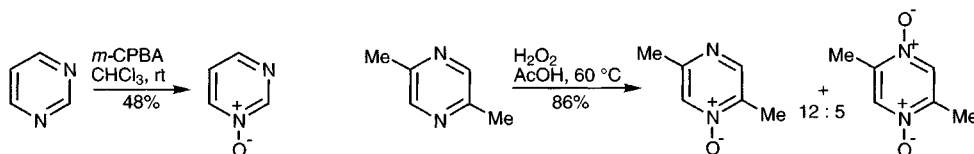
is known as the 'α effect' and is also responsible, for example, for the relatively higher reactivity of hydrogen peroxide as a nucleophile, compared with water.

Unsymmetrically substituted diazines can give rise to two isomeric quaternary salts. Substituents influence the orientation mainly by steric and inductive, rather than mesomeric effects. For example, 3-methylpyridazine alkylates mainly at N-1, even though N-2 is the more electron-rich site. Again, quaternisation of 3-methoxy-6-methylpyridazine takes place adjacent to the methyl substituent, at N-1, although mesomeric release would have been expected to favour attack at N-2.<sup>9</sup>



### 11.1.1.3 Oxidation

All three systems react with peracids,<sup>10</sup> giving *N*-oxides, but care must be taken with pyrimidines<sup>11</sup> due to the relative instability of the products under the acidic conditions. Pyrazines<sup>10</sup> form *N,N'*-dioxides the most easily, but pyridazine<sup>12</sup> requires forcing conditions and pyrimidines, apart from some examples in which further activation is present, give poor yields.<sup>13</sup>



The regiochemistry of *N*-oxidation of substituted azines is governed by the same factors as alkylation (section 11.1.1.2), for example 3-methylpyridazine gives the 1-oxide as main (3:1) product,<sup>14</sup> but the pattern is not a simple one, for 4-methylpyrimidine *N*-oxidises principally (3.5:1) at the nitrogen adjacent to the methyl.<sup>15</sup> The acidity of the medium can also influence the regiochemistry of oxidation, for example 3-cyanopyridazine reacts at N-1 with peracetic acid, but under strongly acidic conditions, in which the heterocycle is mainly present as its N-1-protonic salt, oxidation, apparently involving attack on this salt, occurs at N-2.<sup>16</sup>

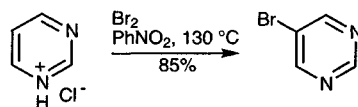
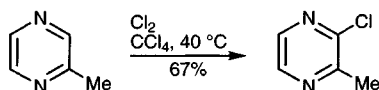
## 11.1.2 Substitution at carbon

Recalling the resistance of pyridines to electrophilic substitution, it is not surprising to find that introduction of a second azomethine nitrogen, in any of the three possible orientations, greatly increases this resistance: no nitration or sulfonation of a diazine or simple alkylidiazine has been reported, though some halogenations are known. It is to be noted that C-5 in pyrimidine is the only position, in all three diazines, which is not in an α- or γ-relationship to a ring nitrogen, and is therefore equivalent to a β-position in pyridine. Diazines carrying electron-releasing (activating) substituents undergo electrophilic substitution much more easily (sections 11.10.2.1 and 11.11).

### 11.1.2.1 Halogenation

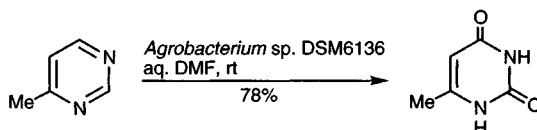
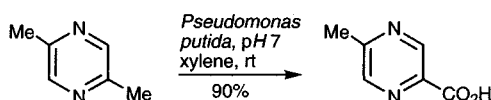
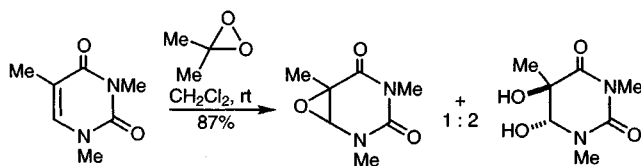
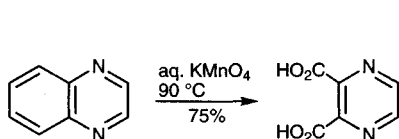
Chlorination of 2-methylpyrazine occurs under such mild conditions that it is almost certain that an addition/elimination sequence is involved, rather than a classical

aromatic electrophilic substitution.<sup>17</sup> Halogenation of pyrimidines may well also involve such processes.<sup>18</sup>



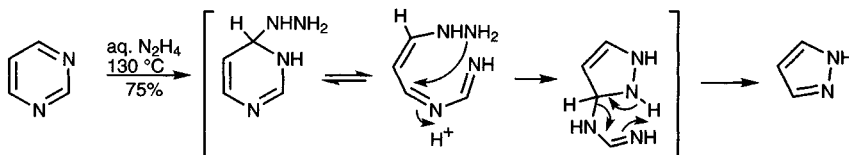
## 11.2 Reactions with oxidising agents

The diazines are generally resistant to oxidative attack at ring carbons, though alkaline oxidising agents can bring about degradation *via* intermediates produced by initial nucleophilic addition (section 11.3). Alkyl substituents<sup>19</sup> and fused aromatic rings<sup>20</sup> can be oxidised to carboxylic acid residues, leaving the heterocyclic ring untouched. An oxygen can be introduced into pyrimidines at vacant C-2 and/or C-4 positions using various bacteria.<sup>21</sup> Dimethyldioxirane converts *N,N*-dialkylated uracils into 5,6-diols probably via 5,6-epoxides.<sup>22</sup>



## 11.3 Reactions with nucleophilic reagents

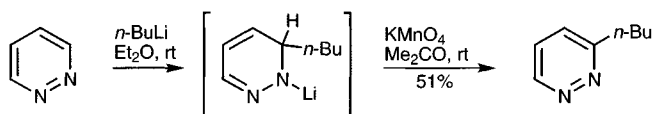
The diazines are very susceptible to nucleophilic addition: pyrimidine, for example, is decomposed when heated with aqueous alkali by a process which involves hydroxide addition as a first step, and it is converted into pyrazole by reaction with hydrazine.



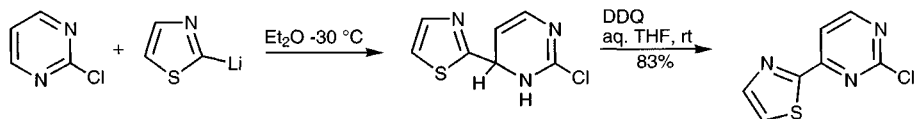
### 11.3.1 With replacement of hydrogen

#### 11.3.1.1 Alkylation and arylation

The diazines readily add alkyl- and aryllithiums, and Grignard reagents, to give dihydro-adducts which can be aromatised by oxidation with reagents such as potassium permanganate or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. In reactions with organolithiums, pyrimidines react at C-4,<sup>13</sup> and pyridazines at C-3, but Grignard reagents add to pyridazines at C-4.<sup>23</sup>



An important point is that in diazines carrying chlorine or methylthio substituents, attack does not take place at the halogen- or methylthio-bearing carbon; halogen-<sup>24</sup> and methylthio-containing<sup>25</sup> products are therefore obtained.

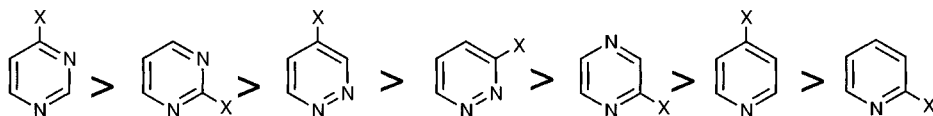


### 11.3.1.2 Amination

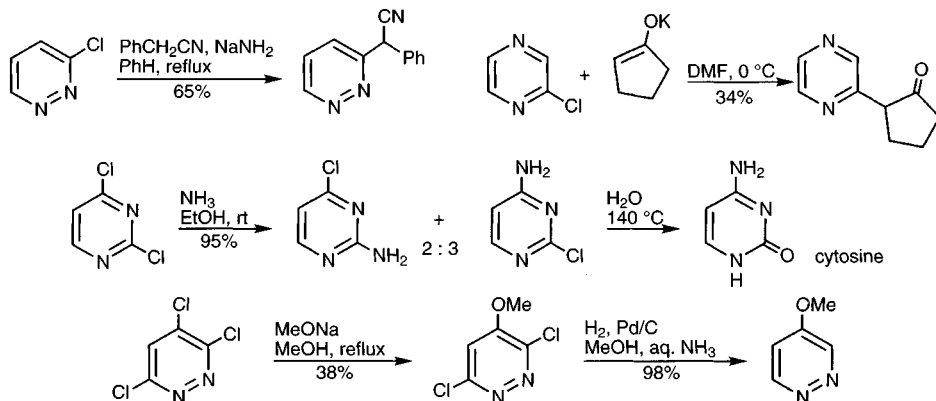
The Chichibabin reaction can be carried out under the usual conditions in a few cases,<sup>26</sup> but is much less general than for pyridines. This may be a consequence of the lower aromaticity of the diazines for, although the initial addition is quite easy, the subsequent loss of hydride (rearomatisation) is difficult. However, high yields of 4-aminopyridazine, 4-aminopyrimidine and 2-aminopyrazine can be obtained by oxidation of the dihydro-adduct *in situ* with potassium permanganate.<sup>27</sup>

### 11.3.2 With replacement of good leaving groups

All the halodiazines, apart from 5-halopyrimidines, react readily with 'soft' nucleophiles such as amines, thiolates, and malonate anions, with substitution of the halide. All cases are more reactive than 2-halopyridines: the relative reactivity can be summarised:



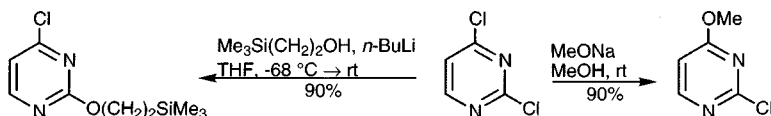
and is illustrated by the following examples:<sup>28</sup>



Nucleophilic displacement of halogen with ammonia<sup>29</sup> and amines<sup>30</sup> can be accelerated by carrying out the displacements in acid solution, when the protonated heterocycle is more reactive than the neutral heterocycle.<sup>31</sup> Halogen can also be easily removed hydrogenolytically, for example treatment of 2,4-dichloropyrimidine,

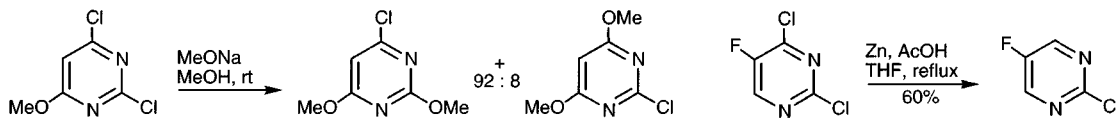
readily available from uracil, with hydrogen in the presence of palladium, or with hydrogen iodide, gives pyrimidine itself.<sup>32</sup>

The difference in reactivity between 2- and 4-halopyrimidines is relatively small and a discussion of the selectivity in nucleophilic displacement reactions of 2,4-dichloropyrimidine (an important synthetic intermediate) is instructive.

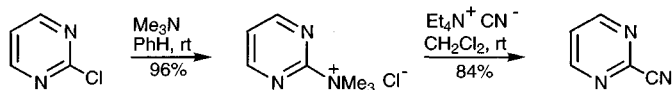


Reaction with sodium methoxide in methanol is highly selective for the 4-chloro substituent<sup>33</sup> whereas, lithium 2-(trimethylsilyl)ethoxide is equally selective, but for the 2-chloro substituent.<sup>34</sup> The former is the normal situation for nucleophilic displacements<sup>35</sup> – 4-chloro > 2-chloro – the second case is the exception where strong co-ordination of lithium in a non-polar solvent to the more basic nitrogen, N-1, leads to activation, and possibly also internal attack, at C-2. Under acidic conditions, an approximately 1:1 mixture of the two methoxy products is formed. Here, hydrogen bonding to the proton on N-1 provides the mechanism for encouraging attack at C-2. Selectivity with other nucleophiles is dependent on the nature of the nucleophile and on reaction conditions.

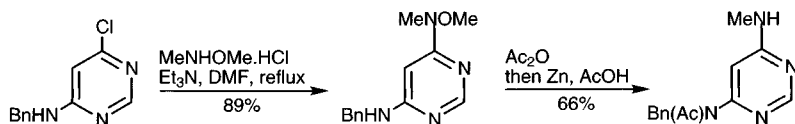
These reactions are also sensitive to the presence of other substituents in the ring, either by electronic or steric effects and this sometimes leads to a reversal of the typical selectivity<sup>36</sup> as can changes in the nucleophile, for example tri-*n*-butylstannyl lithium attacks 2,4-dichloropyrimidine at C-2.<sup>37</sup> Selective reductions are also possible.<sup>38</sup>



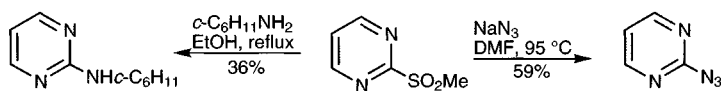
A device which is also used in pyridine and purine chemistry is the initial replacement of halogen with a tertiary amine, the resulting salt now having a better leaving group, as shown below.<sup>39</sup>



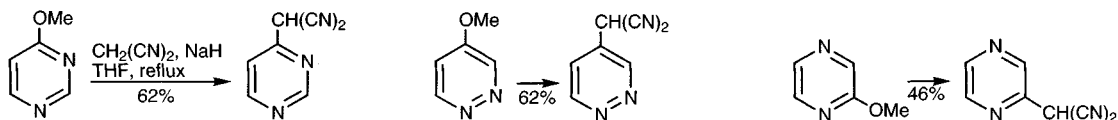
Halopyrimidines with other electron-donating substituents in the ring tend to be much less reactive to nucleophilic substitution: in one example this was overcome by use of the very nucleophilic *O,N*-dimethylhydroxylamine, followed by hydrogenolysis to reveal the amine.<sup>40</sup>



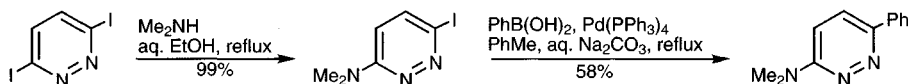
A methanesulfonyl group (as methanesulfonate) is also a good leaving group in all of the diazines,<sup>41</sup> generally better than chloro, sometimes considerably so, for example 3-methanesulfonylpyridazine reacts 90 times faster with methoxide than does 3-chloropyridazine. Sulfonates can be used to catalyse displacements of chlorine via the intermediacy of the sulfone.<sup>42</sup>



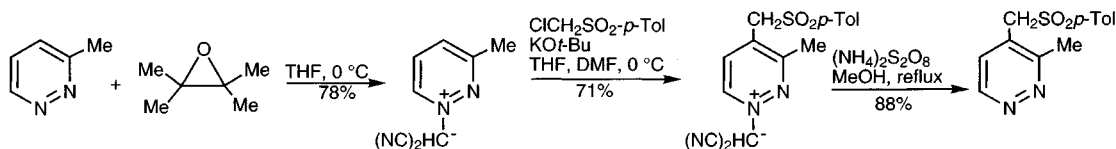
Even methoxy groups can be displaced by carbanions.<sup>43</sup>



Monsubstitution of 2,6-diiodopyridazine is easy, further manipulation via various palladium-catalysed couplings (see also 11.5.2) providing a good route to 2,6-disubstituted pyridazines.<sup>44</sup>



A highly regioselective VNS substitution (section 2.3.3) can be carried out on pyridazines bearing a 3-substituent. Here, formation of a dicyanomethylene ylide only at N-1, due to hindrance of N-2, results in a specific activation of the hindered 4-position.<sup>45</sup>



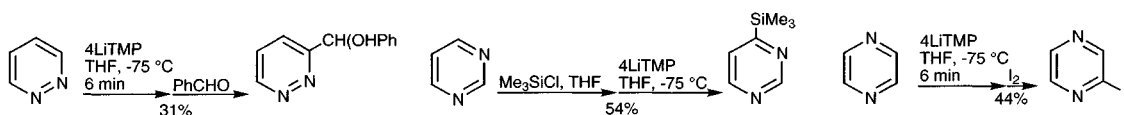
## 11.4 Reactions with bases

### 11.4.1 Deprotonation of C-hydrogen

All three diazines undergo H/D exchange at all ring positions with MeONa/MeOD at 164 °C;<sup>46</sup> the transient carbanions which allow the exchange are formed somewhat faster than for pyridines, and again this is probably due to the acidifying, additional inductive withdrawal provided by the second nitrogen.

### 11.4.2 Metallation

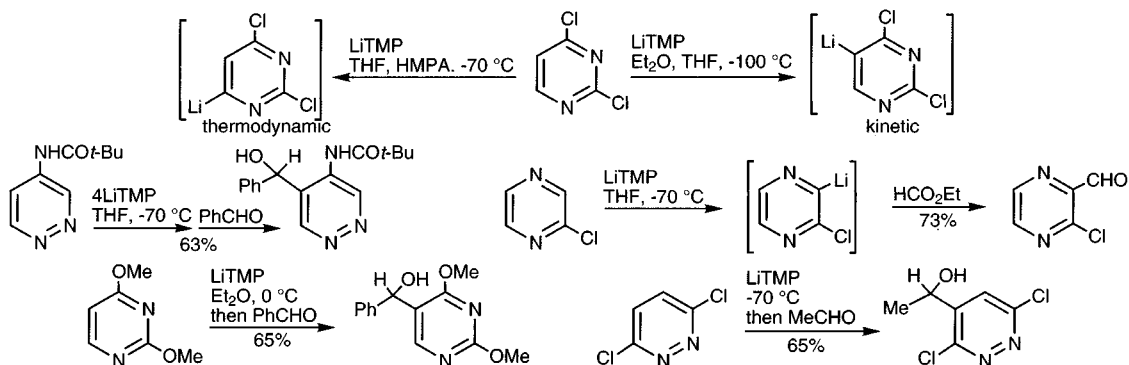
The three parent diazines have been metallated adjacent to nitrogen (for pyrimidine at C-4, not C-2) using the non-nucleophilic lithium tetramethylpiperidide, but the resulting heteroaryllithiums are very unstable, readily forming dimeric compounds by self addition. Moderate to good yields of trapped products can however be obtained either by using very short lithiation times (pyridazine and pyrazine) or by *in situ* trapping where the electrophile is added *before* the metallating agent.<sup>47</sup> 4-Lithiopyridazine has been prepared by transmetalation of the corresponding tri-*n*-butylstannane using *n*-butyllithium. Lithiation of diazines with directing groups (chloro, fluoro, methoxy, methylthio, and various carboxamides) is straightforward<sup>48</sup> and such derivatives have been widely used (see below).



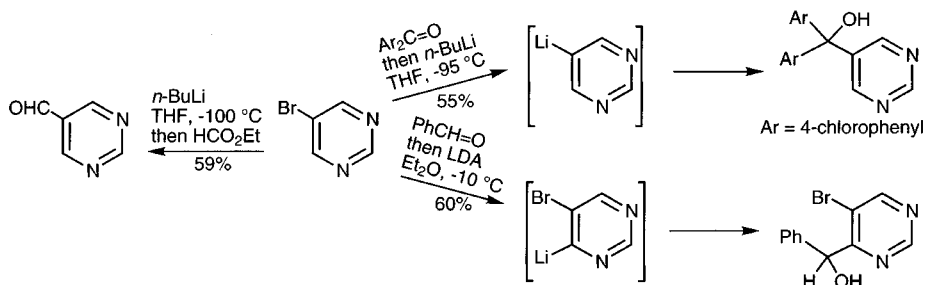
## 11.5 Reactions of C-metallated diazines

### 11.5.1 Lithium derivatives

Typically, lithium tetramethylpiperidide has been used for the kinetically-controlled metallation of substituted diazines;<sup>49</sup> in some cases the use of a somewhat higher temperature allows equilibration to a thermodynamic anion.<sup>50</sup>



Lithiodiazines can also be prepared by halogen exchange with alkylolithiums, but very low temperatures must be used in order to avoid nucleophilic addition to the ring.<sup>51</sup> The examples below show how 5-bromopyrimidine can be lithiated at C-4, using LDA, or alternatively can be made to undergo exchange, using *n*-butyllithium.<sup>52</sup> Note, also, that in some cases, reactions are carried out by adding the electrophile to the pyrimidine *before* lithiation, a practice which incidentally illustrates that metal-halogen exchange with *n*-butyllithium is faster than the addition of *n*-butyllithium to a carbonyl compound.<sup>53</sup>

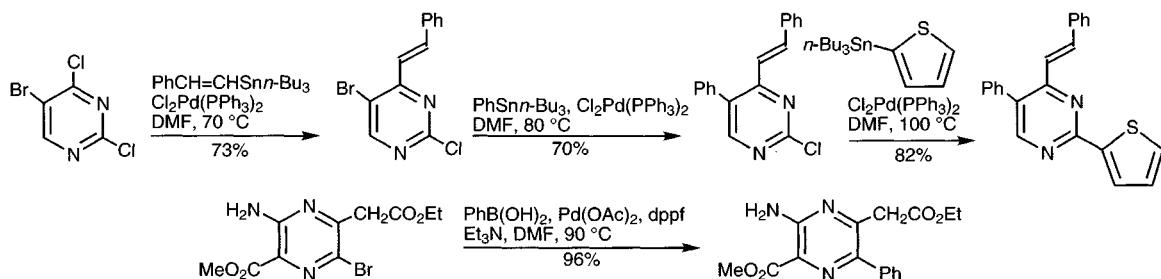


Lithiopyrimidines, -pyrazines, and -pyridazines have been converted by exchange with zinc chloride into the more stable zinc compounds<sup>54</sup> for use in palladium-catalysed couplings (section 11.5.2). Magnesium derivatives have been prepared by reaction of 5-bromopyrimidines with *n*-butylmagnesium bromide and cerium compounds (which give better results than lithiopyrimidines in reactions with enolisable ketones) can be prepared from either bromo- or lithiopyrimidine.<sup>55</sup>

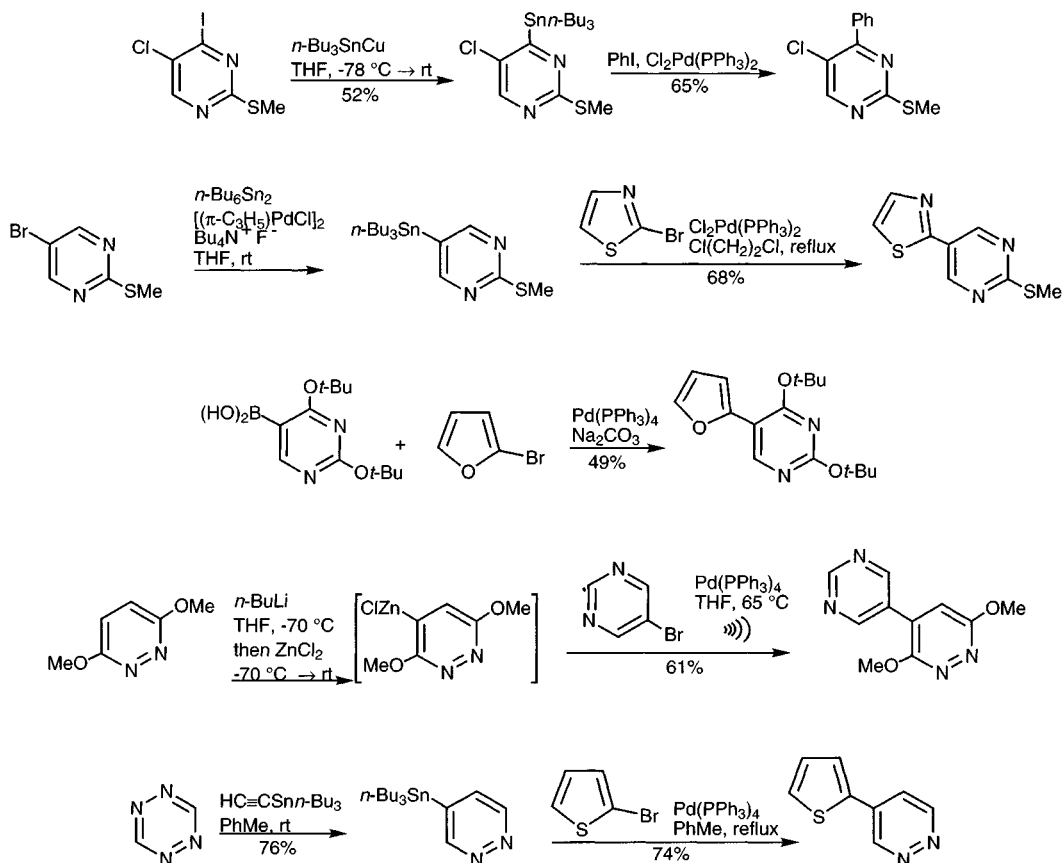
### 11.5.2 Palladium-catalysed reactions

Palladium- (and nickel-) -catalysed coupling reactions proceed normally on halodiazines and the equivalent triflates,<sup>56</sup> the most significant feature being the enhanced reactivity relative to chlorobenzenes of chlorine at position  $\alpha$  and  $\gamma$  to a nitrogen, just as in pyridine chemistry. In some particularly activated cases, this extra activation is sufficient to overcome the normally higher reactivity of bromine, but not

of iodine.<sup>57</sup> In the examples shown below the 4-chlorine has the edge over the bromine, although the reagent needed careful selection for good selectivity. The same selectivity in reactivity of pyrimidines for nucleophilic substitution ( $4 > 2$ ) applies in palladium-catalysed reactions.<sup>58</sup>



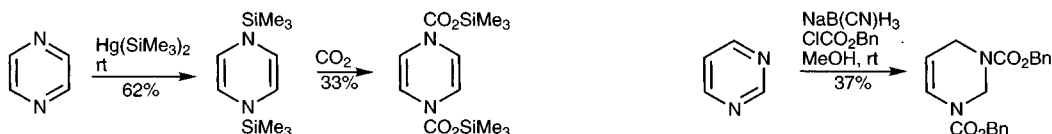
In diazine chemistry, tin compounds have normally been used<sup>59</sup> when an organometallic derivative of the heterocycle is required for a coupling reaction; they have the particular advantage that they can be prepared without the use of an organolithium intermediate. Boronic acids have been used occasionally,<sup>60</sup> but as a general rule they are difficult to prepare at positions  $\alpha$  to azine nitrogens – a major disadvantage in diazine chemistry. Zinc compounds have advantages in some cases. A selection of examples involving palladium(0)-catalysed couplings is shown below.



## 11.6 Reactions with reducing agents

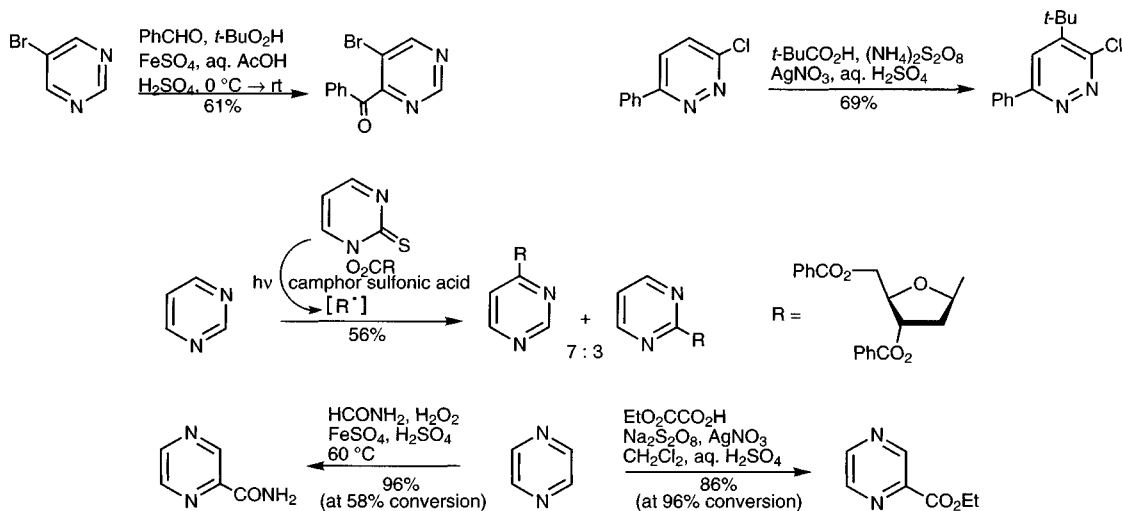
Due to their lower aromaticity, the diazines are more easily reduced than pyridines. Pyrazine and pyridazine can be reduced to hexahydro derivatives with sodium in hot ethanol; under these conditions pyridazine has a tendency for subsequent reductive cleavage of the N–N bond.

Partial reductions of quaternary salts to dihydro compounds can be achieved with borohydride but such processes are much less well studied than in pyridinium salt chemistry.<sup>61</sup> 1,4-Dihydropyrazines have been produced with either silicon<sup>62</sup> or amide<sup>63</sup> substitution at the nitrogen atoms, and all the diazines can be reduced to tetrahydro-derivatives with carbamate protection on nitrogen, which aids in stabilisation and thus allows isolation.<sup>64</sup>



## 11.7 Reactions with radical reagents

Radicals add readily to diazines under Minisci conditions.<sup>65</sup> Additions to pyrimidine often show little selectivity, C-2 *versus* C-4, however a selective Minisci reaction on 5-bromopyrimidine provided a convenient synthesis of the 4-benzoyl derivative on a large scale;<sup>66</sup> attack at C-5 does not take place.<sup>67</sup> Radical attack on pyridazines shows selectivity for C-4,<sup>68</sup> even when C-3 is unsubstituted. Pyrazines<sup>69</sup> can of course substitute in only one type of position.

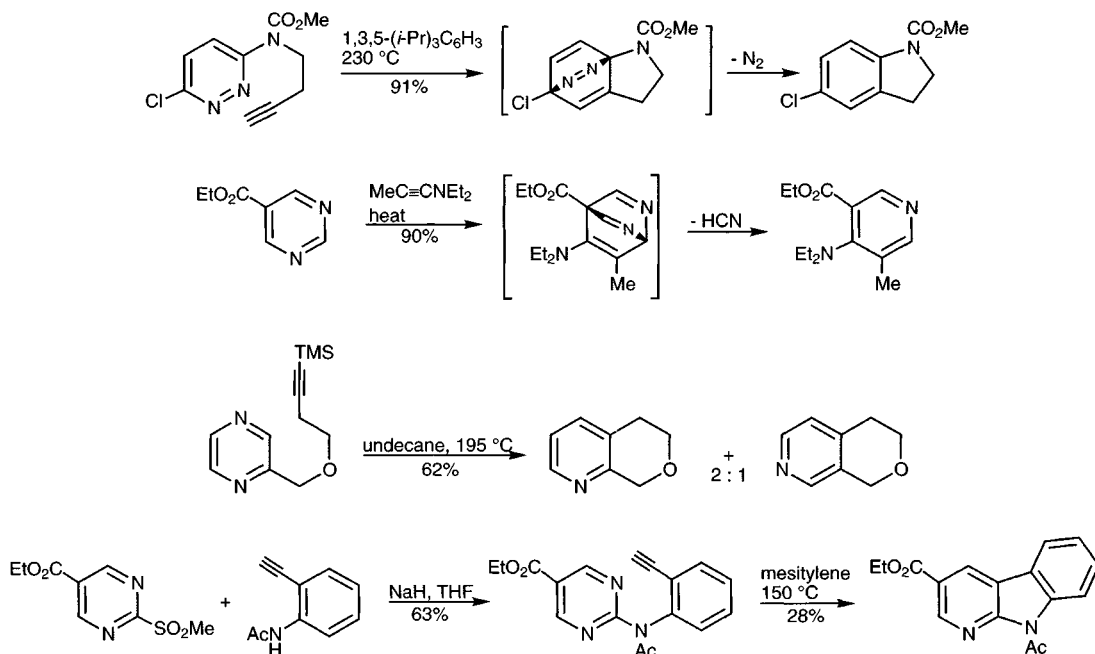


Substitutions of halide by an  $\text{S}_{\text{RN}}1$  mechanism (section 5.9) have been carried out, but addition/elimination mechanisms compete in the more reactive halides.<sup>70</sup>

## 11.8 Electrocyclic reactions

All the diazines, providing they also have electron-withdrawing substituents, undergo Diels-Alder additions with dienophiles. Intramolecular reactions occur the most

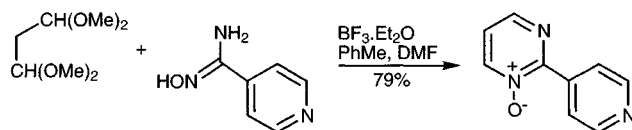
readily; these do not even require the presence of activating substituents. The immediate products of such process usually lose nitrogen (pyridazine adducts) or hydrogen cyanide (adducts from pyrimidines and pyrazines) to generate benzene and pyridine products,<sup>71</sup> respectively, as illustrated below.<sup>72</sup> Singlet oxygen has been added across the 2,5-positions of pyrazines.<sup>73</sup>



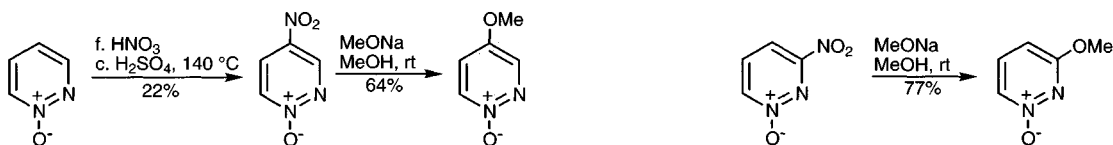
All three diazines undergo dipolar addition to the imine unit with benzonitrile *N*-oxide, the initial mono-adducts then undergoing further transformations.<sup>74</sup>

## 11.9 Diazine *N*-oxides<sup>75</sup>

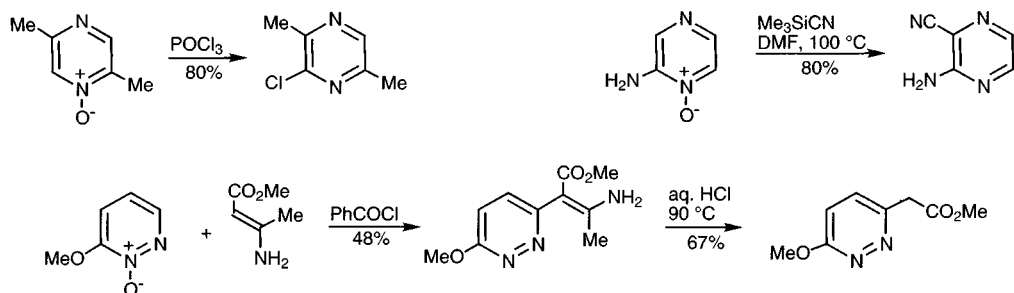
Although pyridazine and pyrazine *N*-oxides can be readily prepared by oxidation of the parent heterocycles, pyrimidine *N*-oxides are more difficult to obtain in this way but they can conveniently be prepared by ring synthesis.<sup>76</sup>



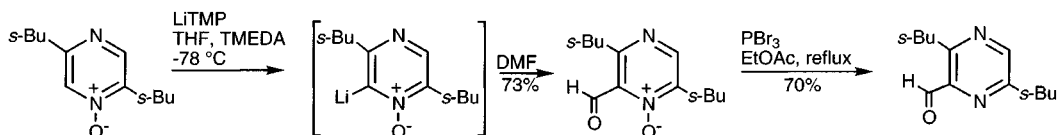
Pyridazine and pyrazine *N*-oxides behave like their pyridine counterparts in electrophilic substitution,<sup>77</sup> and nucleophilic displacement reactions involving loss of the oxygen. It is interesting that displacement of nitro  $\beta$  to the *N*-oxide function occurs about as readily as that of a  $\gamma$  nitro group, but certainly, displacements on *N*-oxides proceed faster<sup>78</sup> than for the corresponding base.



Nucleophilic substitution by halide, cyanide, carbon nucleophiles such as enamines, and acetate (by reaction with acetic anhydride), with concomitant loss of the oxide function occurs smoothly in all three systems,<sup>79</sup> though the site of introduction of the nucleophile is not always that ( $\alpha$  to the *N*-oxide) predicted by analogy with pyridine chemistry, as illustrated by a couple of the examples below.<sup>13</sup>

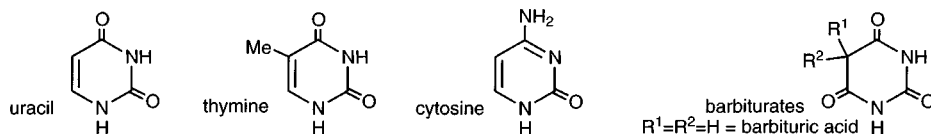


The *N*-oxide grouping can also serve as an activating substituent to allow regioselective lithiation<sup>80</sup> or for the further acidification (section 11.12) of side-chain methyl groups for condensations with, for example, aromatic aldehydes or amyl nitrite.<sup>81</sup>



## 11.10 Oxydiazines

By far the most important naturally occurring diazines are the pyrimidones uracil, thymine, and cytosine, which as the nucleosides uridine, thymidine and cytidine, are components of the nucleic acids. As a consequence, a great deal of synthetic chemistry has been directed towards these types of compound in the search for antiviral and anti-tumour agents.<sup>82</sup> Among other well known pyrimidones are the barbiturate sedatives.<sup>83</sup>

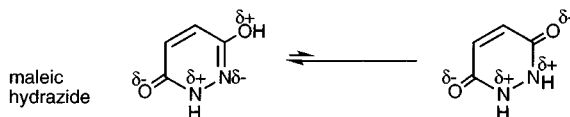


### 11.10.1 Structure of oxydiazines

With the exception of 5-hoxypyrimidine, which is analogous to 3-hydroxypyridine, all the mono-oxygenated diazines exist predominantly as carbonyl tautomers and are thus categorised as diazinones.

The dioxydiazines present a more complicated picture, for in some cases, where both oxygens are  $\alpha$  or  $\gamma$  to a nitrogen, and both might be expected to exist in carbonyl form, one actually takes up the hydroxy form: a well known example is 'maleic hydrazide'. One can rationalise the preference easily in this case, as resulting from the removal of the unfavourable interaction between two adjacent, partially positive nitrogen atoms in the dicarbonyl form. On the other hand, uracil exists as the

dione and most of its reactions<sup>84</sup> can be interpreted on this basis. Barbituric acid adopts a tricarbonyl tautomeric form.



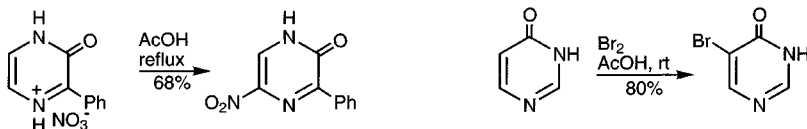
### 11.10.2 Reactions of oxydiazines

For many synthetic transformations, it is convenient to utilise halo- or alkoxydiazines, in lieu of the (oxidation level) equivalent -ones; often this device facilitates solubility; a final hydrolysis re-converts to the 'one'.

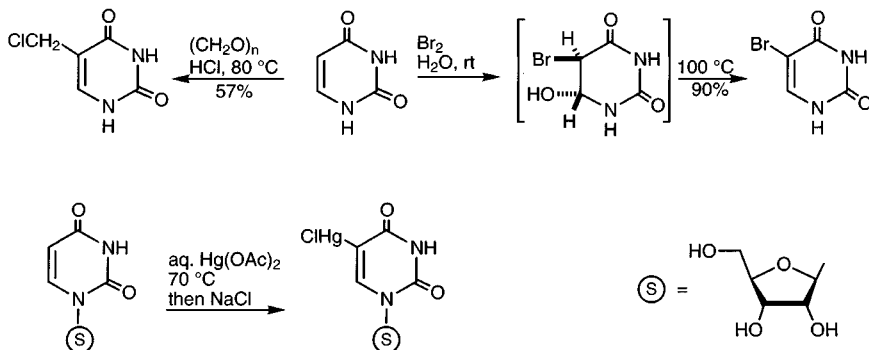
#### 11.10.2.1 Reactions with electrophilic reagents

The deactivating effect of two ring nitrogens cannot always be overcome by a single oxygen substituent: 3-pyridazinone can be neither nitrated nor halogenated, or again, of the singly oxygenated pyrimidines, only 2(1*H*)-pyrimidone can be nitrated;<sup>85</sup> pyrazinones seem to be the most reactive towards electrophilic substitution.

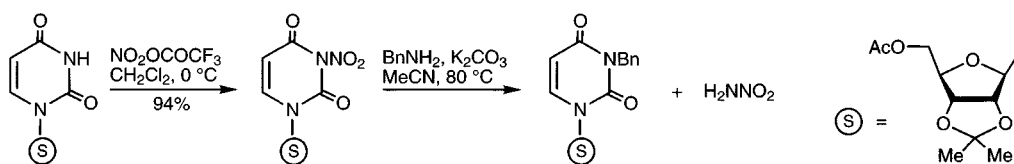
5-Hydroxypyrimidine, the only phenolic diazine, is unstable even to dilute acid and no electrophilic substitutions have been reported.



Uracils undergo a range of electrophilic substitution reactions such as halogenation,<sup>86</sup> phenylsulfenylation,<sup>86</sup> mercuration,<sup>87</sup> and hydroxy- and chloromethylation.<sup>88</sup> Bromination of uracils has been shown to proceed *via* the bromohydrin adduct, and similarly of 2-pyrimidone, *via* the bromohydrin-hydrate;<sup>89</sup> iodine with tetrabutylammonium peroxydisulfate allows iodination.<sup>90</sup>

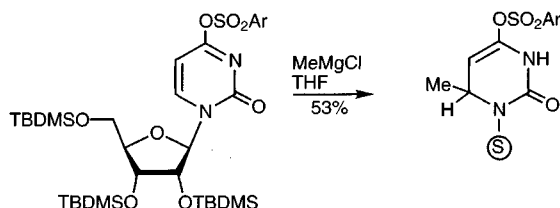


Uracil derivatives can be nitrated at C-5 under conditions which allow retention of a sugar residue at N-1. Nitration at N-3 can also be achieved: N-3-nitro compounds react with amines via an ANRORC mechanism, with displacement of nitramide and incorporation of the amine as a substituted N-3. This sequence has been utilised to prepared <sup>15</sup>N N-3-labelled pyrimidines and is illustrated below.<sup>91</sup>

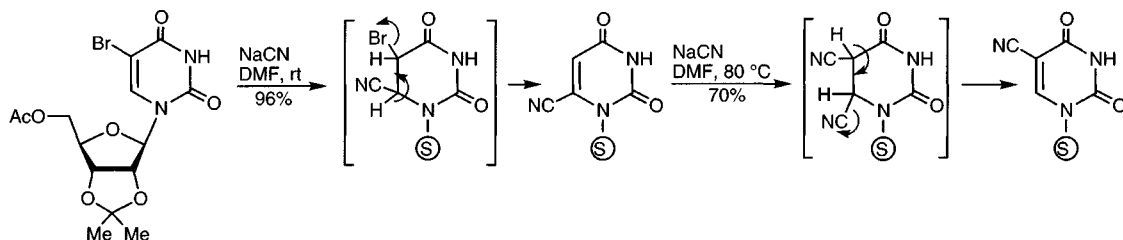


### 11.10.2.2 Reactions with nucleophilic reagents

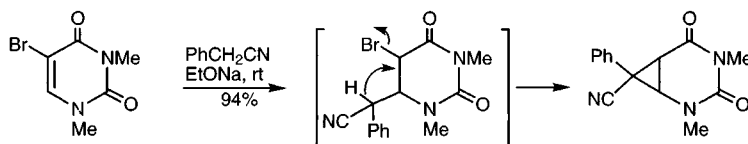
Diazinones are quite susceptible to nucleophilic attack, reaction taking place generally *via* Michael-type adducts rather than by attack at a carbonyl group, though there are exceptions<sup>92</sup> to this generalisation. Grignard reagents add to give dihydro-compounds and good leaving groups can be displaced.<sup>93</sup>



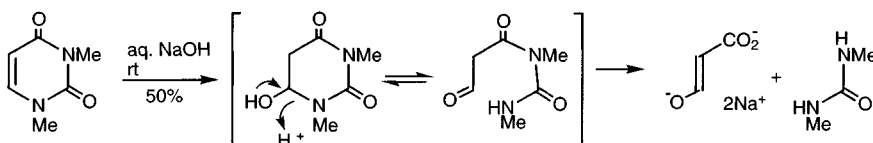
The reaction of cyanide with a protected 5-bromouridine<sup>94</sup> is instructive: under mild conditions a *cine*-substituted product is obtained *via* a Michael addition followed by  $\beta$ -elimination of bromide, but at higher temperatures, conversion of the 6- into the 5-cyano isomer is observed, i.e. the product of apparent, direct displacement of bromide is obtained. The higher temperature product arises *via* an isomerisation involving another Michael addition then elimination of the 6-cyano group.



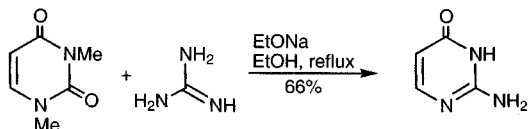
In a related reaction with the anion of phenylacetonitrile, the initial addition is followed by an internal alkylation, generating a cyclopropane.<sup>95</sup>



The conversion of 1,3-dimethyluracil into a mixture of  $N,N'$ -dimethylurea and the disodium salt of formylacetic acid begins with the addition of hydroxide at C-6.<sup>96</sup>



The propensity for uracils to add nucleophiles can be put to synthetic use by reaction with double nucleophiles such as ureas, when a sequence of addition, ring opening and reclosure can achieve (at first sight) extraordinary transformations.<sup>97</sup>



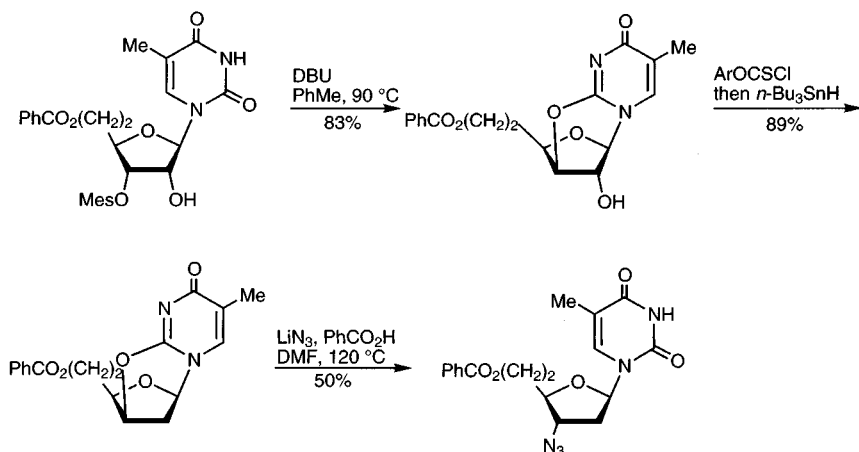
### 11.10.2.3 Reactions with bases

#### N-Deprotonation

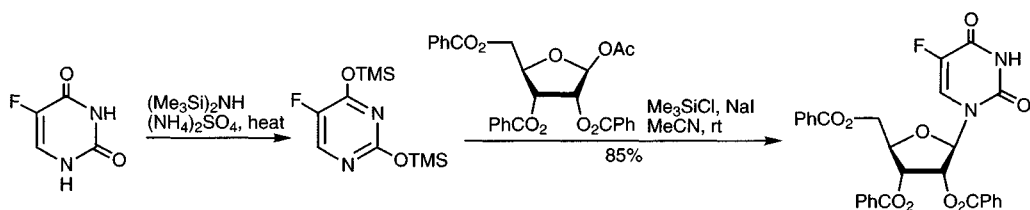
Like pyridones, oxydiazines are readily deprotonated under mild conditions to give ambident anions which can be alkylated, conveniently by phase-transfer methods, alkylation usually occurring at nitrogen.<sup>98</sup> 3-Pyridazinones alkylate cleanly on N-2 under phase-transfer conditions<sup>99</sup> but the regiochemistry of uracil alkylation is sometimes difficult to control (see also below). Carbon substitution can also be effected in some cases *via* delocalised *N*-anions, as in the reaction of 6-methyluracil with formaldehyde,<sup>100</sup> or with diazonium salts.<sup>101</sup>



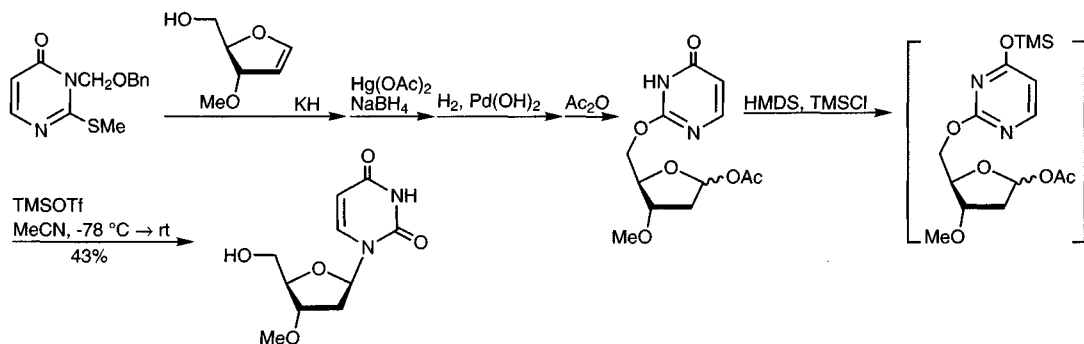
*O*-Alkylation is also possible and is particularly important in ribosides where it occurs intramolecularly and can be used to control the stereochemistry of substitution in the sugar residue as illustrated in the following sequence for replacement of the 3'-hydroxyl with azide and with overall retention of configuration.<sup>102</sup>



Alternative methods for *N*-alkylation include heating with trimethyl phosphate<sup>103</sup> and the alkylation of *O*-silylated derivatives,<sup>104</sup> which is an important method for unambiguous *N*-alkylation especially ribosylation of uracils;<sup>105</sup> ribosylation is subject to the same stereochemical difficulties as in purine chemistry (for further discussion see section 24.2.1.2).

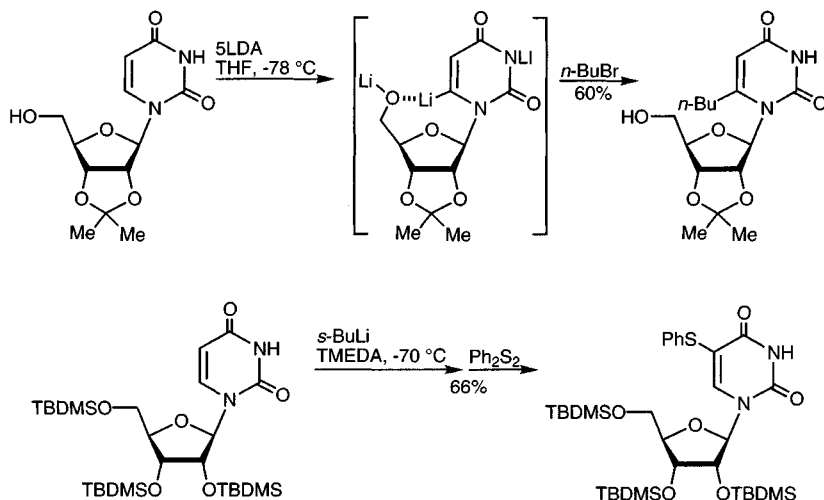


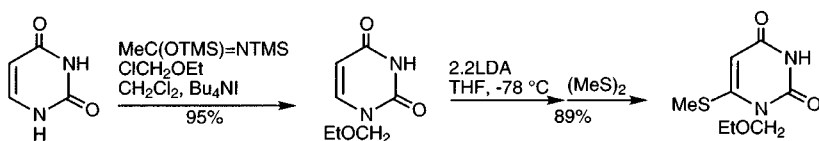
Stereospecific ribosylation of uracils and other pyrimidine bases has been carried out by attachment to the 5-hydroxymethyl substituent of the sugar, followed by internal delivery to C-2.<sup>106</sup>



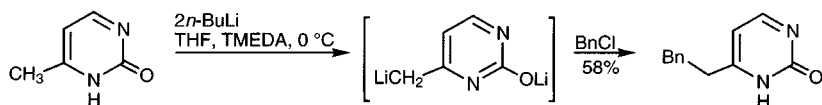
## C-Metallation

C-Lithiation of uridine derivatives has been thoroughly studied as a means for the introduction of functional groups at C-5 and C-6. Chelating groups at C-5' (hydroxyl or methoxymethoxy) favour 6-metallation,<sup>107</sup> as do equilibrating conditions, indicating that this is the most stable lithio-derivative. Kinetic lithiation, at C-5, can be achieved when weakly chelating silyloxy groups are used as protecting groups for the sugar.<sup>108</sup> It is remarkable that protection of the N-H group is not necessary and this is illustrated again in the 6-lithiation of uracil carrying an ethoxymethyl substituent on N-1.<sup>109</sup>

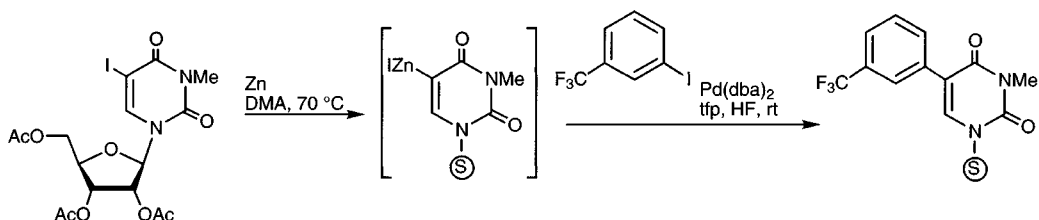




NH-Protection is also unnecessary for the side-chain metallation of 6-methylpyrimidin-2-one.<sup>110</sup>

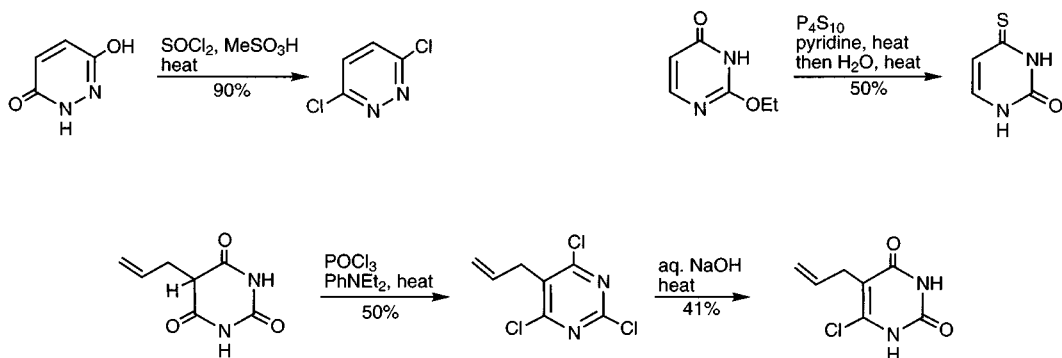


Zinc derivatives of uracils can be prepared directly by reaction of the appropriate halide with zinc dust. They react with a limited range of electrophiles but are particularly useful for palladium-catalysed couplings<sup>111</sup> (see also 11.10.2.5).

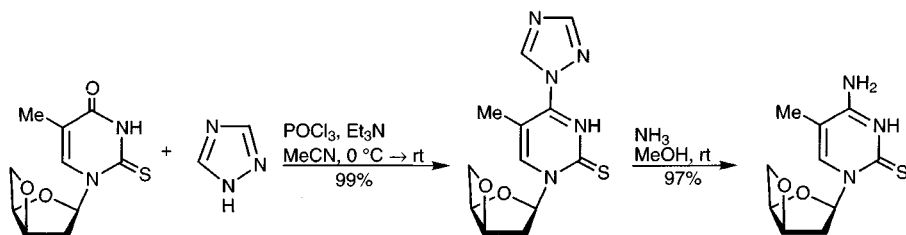


#### 11.10.2.4 Replacement of oxygen

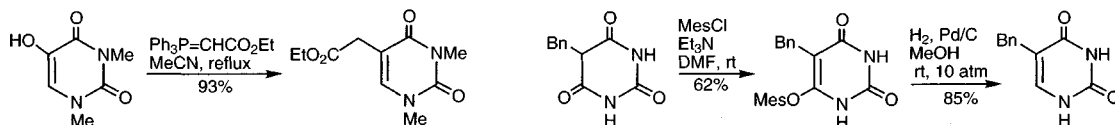
Oxydiazines, with the oxygen  $\alpha$  to nitrogen, can be converted into halo-<sup>29,112</sup> and thio-compounds<sup>113</sup> using the same reagents used for 2- and 4-pyridones, including *N*-bromosuccinimide with triphenylphosphine.<sup>114</sup> The reactions of *O*-silylated pyrazinones with phosphorus(III) bromide or phosphorus(V) chloride are also efficient.<sup>115</sup>



Diazinones can also now be converted directly into aminodiazines, without the (classical) intermediacy of an isolated halo-derivative by various processes including the use of 1,2,4-triazole, as illustrated below.<sup>116</sup>

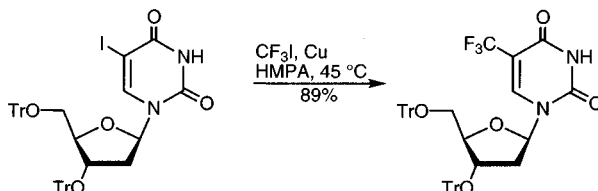
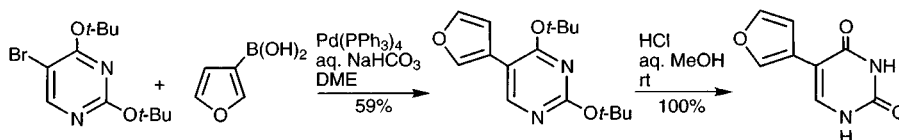
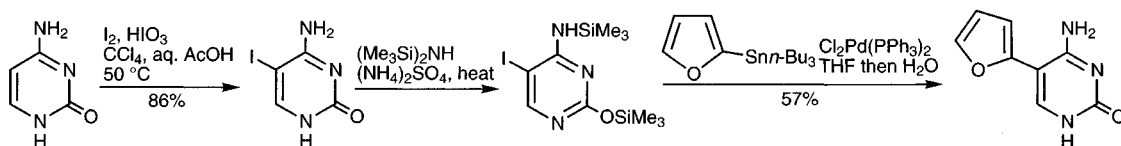


5-Hydroxypyrimidine-2,4-diones react as ketones at the 5-position and undergo Wittig condensation, the double bond thus formed isomerising back into the stabler position in the ring.<sup>117</sup> Barbituric acid and C-5-derivatives can be converted into uracils by first forming a 6-mesylate and then catalytic hydrogenolysis.<sup>118</sup>

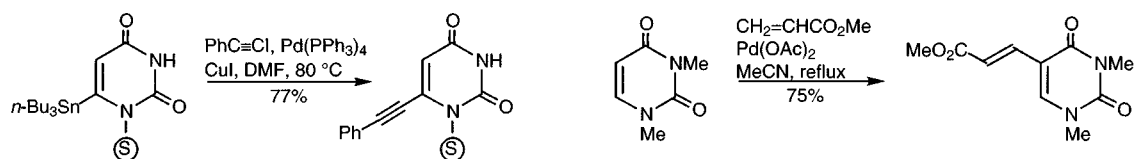


#### 11.10.2.5 Transition metal-catalysed reactions

Halodiazinones undergo palladium-catalysed couplings with boronic acids and stannanes, but the reactions appear to be less consistent than with other systems. Temporary protection as silyl derivatives,<sup>119</sup> or the use of additives such as silver oxide<sup>120</sup> are beneficial in some cases, but it is often preferable to carry out transformations on alkoxydiazines, followed by hydrolysis. Direct coupling with organocopper reagents has also been described.<sup>121</sup>



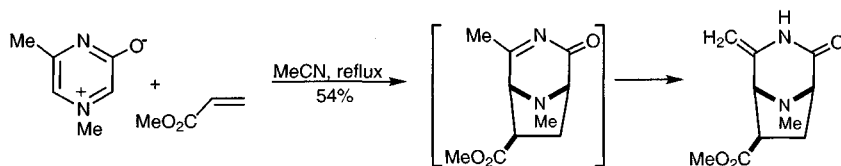
Stannyluridines, prepared via lithiation, have been used in coupling reactions, but again the use of the corresponding dialkoxypyrimidine is usually to be preferred when an organometallic derivative of the heterocycle is required.<sup>122</sup>



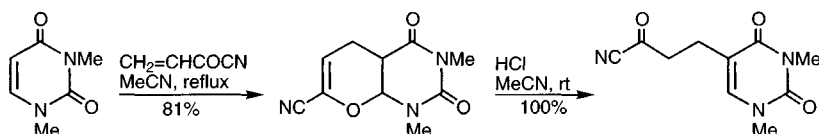
Heck reactions can be carried out on halo- or the readily available mercuri-derivatives, the latter requiring the use of one equivalent of palladium.<sup>123</sup> In addition, due to their susceptibility to electrophilic substitution, 'oxidative' Heck couplings (proceeding via *in situ* palladation) have found use in uracil chemistry, as shown above.<sup>124</sup>

### 11.10.2.6 Electrocyclic reactions

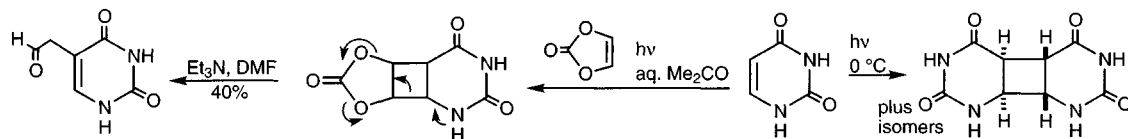
Mesoionic oxidopyraziniums undergo cycloadditions<sup>125</sup> similar to those known for oxidopyridiniums (section 5.8) and oxidopyryliums (section 8.1.7).



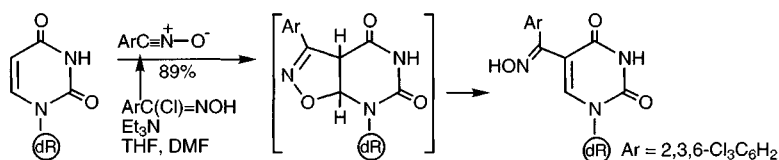
Heterodienophiles have also been studied: diethyl azodicarboxylate adds across the 2,6-positions of a pyridazin-3-one, and singlet oxygen across the 2,5-positions of pyrazinones.<sup>126</sup> The immediate cycloadduct is isolable when acryloyl cyanide is used as the heterodiene component in reaction with a pyrimidine-2,4-dione.<sup>127</sup>



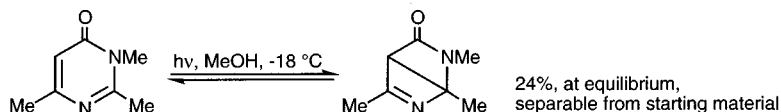
Because of possible relevance to mutagenesis, considerable study has been devoted to study of the photochemical transformations of oxypyrimidines; uracil, for example, takes part in a 2 + 2 cycloaddition with itself,<sup>128</sup> or with vinylene carbonate (1,3-dioxol-2-one).<sup>129</sup> Uracils undergo radical additions;<sup>130</sup> these too are of possible relevance to mutagenesis mechanisms.



The reaction of deoxyuridine with nitrile oxides gives products of apparent electrophilic substitution, but these probably arise by ring opening of a cycloadduct (*cf.* 11.8).<sup>131</sup>

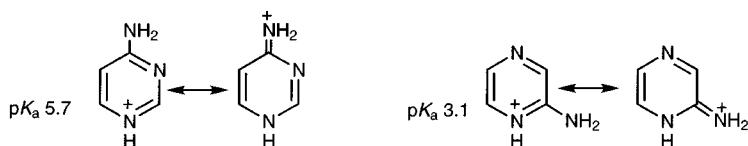


2-Pyrimidones<sup>132</sup> and 4-pyrimidones<sup>133</sup> form bicyclic systems and pyrazine isomerises into pyrimidine, on exposure to light.<sup>134</sup>

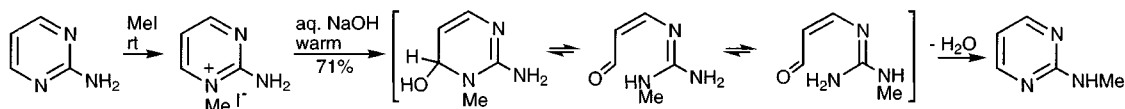


## 11.11 Aminodiazines

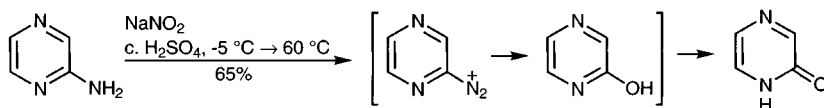
Aminodiazines exist in the amino form. They are stronger bases than the corresponding unsubstituted systems and always protonate on one of the ring nitrogen atoms: where two isomeric cations are possible, the order of preference for protonation is of a ring nitrogen which is  $\gamma > \alpha > \beta$  to the amino group, as can be seen in the two examples below. A corollary of this is that those aminodiazines which contain a  $\gamma$ -aminoazine system are the strongest bases.



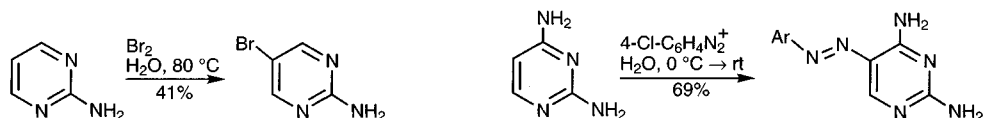
The alkali-promoted rearrangement of quaternary salts derived from 2-aminopyrimidine provides the simplest example of the Dimroth rearrangement.<sup>135</sup> The larger the substituent on the positively charged ring nitrogen the more rapidly the rearrangement proceeds, no doubt as a result of the consequent relief in strain between the substituent and the adjacent amino group.



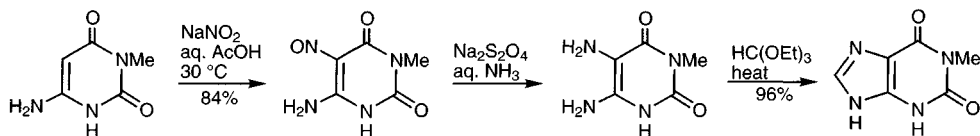
All of the aminodiazines react with nitrous acid to give the corresponding diazonium salts,<sup>29</sup> by way of highly reactive diazonium salts; even 5-aminopyrimidine does not give a stable diazonium salt, though a low yield of 2-chloropyrimidine can be obtained by diazotisation of 2-aminopyrimidine in concentrated hydrochloric acid.<sup>136</sup>



One amino group is sufficient in most cases to allow easy electrophilic substitution, halogenation<sup>137</sup> for example, and two amino groups activate the ring to attack even by weaker electrophilic reagents – for example by thiocyanogen.<sup>138</sup> Diaminopyrimidines will couple with diazonium salts<sup>139</sup> which provides a means for the introduction of a third nitrogen substituent.

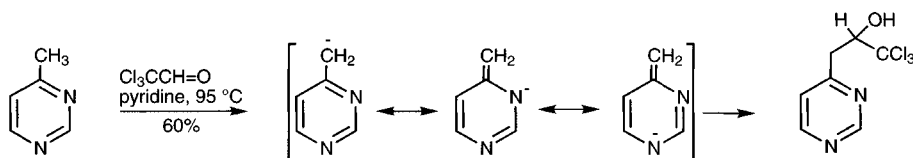


Amino-oxy-pyrimidines,<sup>140</sup> and amino-dioxy-pyrimidines<sup>141</sup> can be C-nitrosated, and such 5,6-dinitrogen-substituted pyrimidines, after reduction to 5,6-diaminopyrimidines, are important intermediates for the synthesis of purines (an example is shown below; see also section 24.13.1.1) and pteridines (section 11.13.4.6).

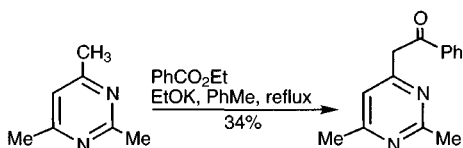


## 11.12 Alkyldiazines

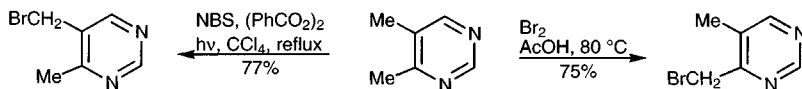
All alkyldiazines, with the exception of 5-alkylpyrimidines, undergo condensations which involve deprotonation of the alkyl group,<sup>142</sup> in the same way as  $\alpha$ - and  $\gamma$ -picolines. The intermediate anions are stabilised by mesomerism involving one, or in the case of 2- and 4-alkylpyrimidines, both nitrogens.



In pyrimidines, a 4-alkyl is deprotonated more readily than a 2-alkyl group;<sup>143</sup> here again one sees the greater stability associated with a  $\gamma$ -quinonoid resonating ion.



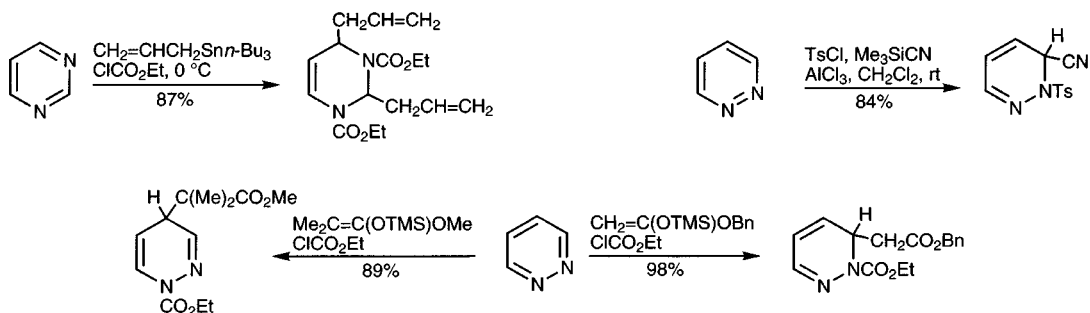
Side-chain radical halogenation selects a pyrimidine 5-methyl over a pyrimidine 4-methyl; the reverse selectivity can be achieved by halogenation in acid solution – presumably an *N*-protonated, side-chain deprotonated species, i.e. the enamine tautomer, is involved.<sup>144</sup>



## 11.13 Quaternary azinium salts

The already high susceptibility of the diazines to nucleophilic addition is greatly increased by quaternisation. Addition of organometallic reagents to *N*-acyl quaternary salts has been achieved in some cases but is much more restricted than is the case with pyridines (section 5.13). Thus, allylstannanes<sup>145</sup> and -silanes<sup>146</sup> and silyl enol ethers have been added to diazine salts (hydride also traps such salts (section 11.6)). Pyridazines give good yields of monoadducts with attack mainly  $\alpha$  to the acylated nitrogen, but the regioselectivity of silyl ether addition<sup>147</sup> is sensitive to substituents. Pyrazine gives mainly double addition products and pyrimidine

produces only the double adduct. Reissert adducts have been described for pyridazine and pyrimidine.<sup>148</sup>



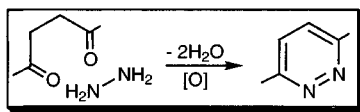
## 11.14 Synthesis of diazines

Routes for the ring synthesis of the isomeric diazines are, as one would expect, quite different one from the other, and must therefore be dealt with separately.

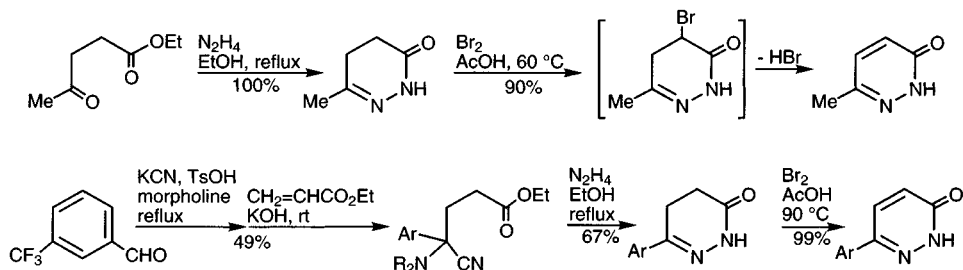
### 11.14.1 Ring synthesis of pyridazines

#### 11.14.1.1 From a 1,4-dicarbonyl compound and a hydrazine

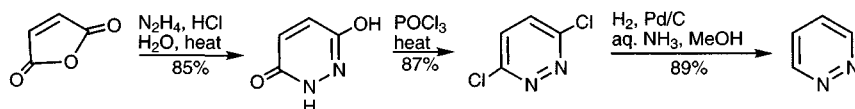
By far the most common method for the synthesis of pyridazines involves a 1,4-dicarbonyl compound reacting with hydrazine; unless the four-carbon component is unsaturated, a final oxidative step is needed to give an aromatic pyridazine.



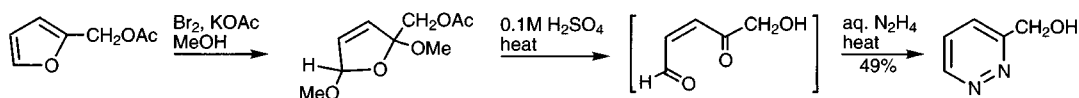
The most useful procedure makes use of a 1,4-keto-ester giving a dihydropyridazinone which can be easily dehydrogenated to the fully aromatic heterocycle, often by *C*-bromination then dehydrobromination;<sup>149</sup> sodium 3-nitrobenzoate as an oxidant is a good alternative if complications would attend the use of halogenation. 6-Arylpyridazinones have been produced by this route in a number of ways: using an  $\alpha$ -amino-nitrile as a masked ketone in the four-carbon component,<sup>150</sup> or by reaction of an acetophenone with glyoxylic acid and then hydrazine.<sup>151</sup> Friedel-Crafts acylation using succinic anhydride is an alternative route to 1,4-keto-acids, reaction with hydrazine again giving 6-arylpyridazinones.<sup>152</sup> Alkylation of an enamine with a phenacyl bromide produces 1-aryl-1,4-diketones allowing synthesis of 3-arylpyridazines.<sup>153</sup>



Maleic anhydride and hydrazine give the hydroxypyridazinone directly,<sup>154</sup> the additional unsaturation in the 1,4-dicarbonyl component meaning that an oxidative step is not required; conversion of 3-hydroxypyridazin-6-one into 3,6-dichloropyridazine makes this useful intermediate very easily available.

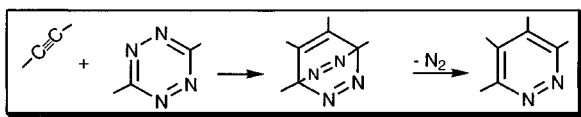


Saturated 1,4-diketones can suffer in this approach from the disadvantage that they can react with hydrazine in two ways, giving mixtures of the desired dihydropyridazine and an *N*-aminopyrrole; this complication does not arise when unsaturated 1,4-diketones are employed.<sup>155</sup> Synthons for unsaturated 1,4-diketones are available as cyclic acetals from the oxidation of furans (section 15.1.4), and react with hydrazines to give the fully aromatic pyridazines directly.<sup>156</sup>

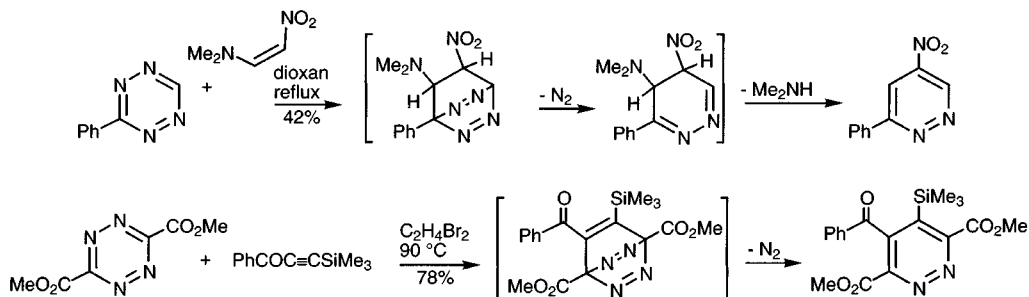


#### 11.14.1.2 By cycloaddition of a 1,2,4,5-tetrazine with an alkyne

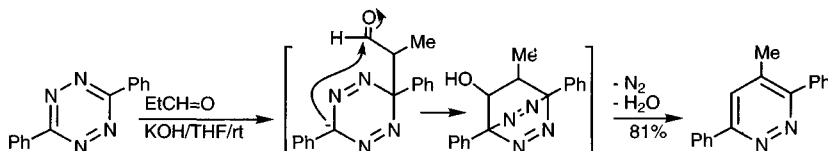
Cycloaddition of a 1,2,4,5-tetrazine with an alkyne (or its equivalent), with elimination of nitrogen gives pyridazines.



This process works best when the tetrazine has electron-withdrawing substituents, but a wide range of substituents can be incorporated on the acetylene, including nitro, trimethylsilyl, and trimethyltin, affording routes to substituted pyridazines<sup>157</sup> not easily available by other methods.



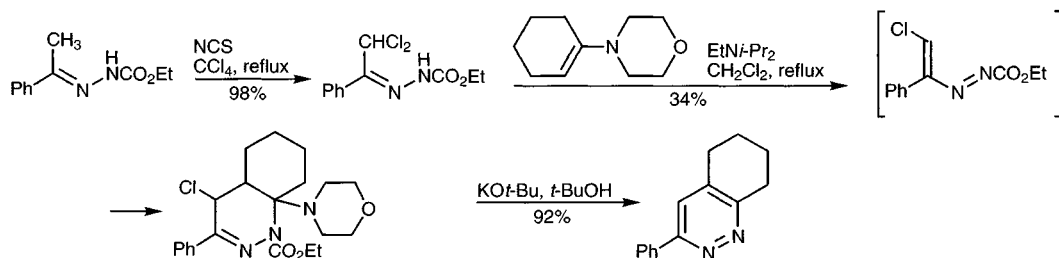
The addition of ketone and aldehyde enolates to tetrazines, though not a concerted process, has the same overall effect.<sup>158</sup>



### 11.14.1.3 By other cycloaddition-based processes

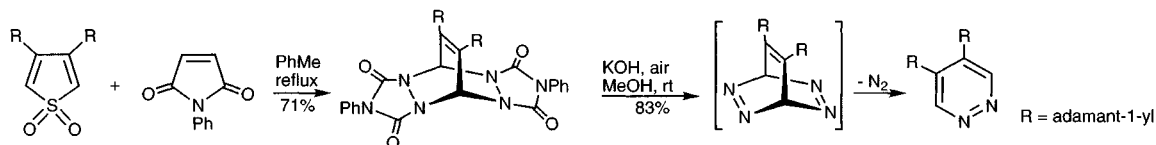
#### 11.14.1.3.1 From halohydrazone

Di- and trihalohydrazone react with enol ethers or enamines in the presence of base to give pyridazines via the intermediacy of an azadiene. The final pyridazine may be formed directly in the reaction mixture or with intermediate di- or tetrahydro-intermediate isolated and further treated with base.<sup>159</sup>



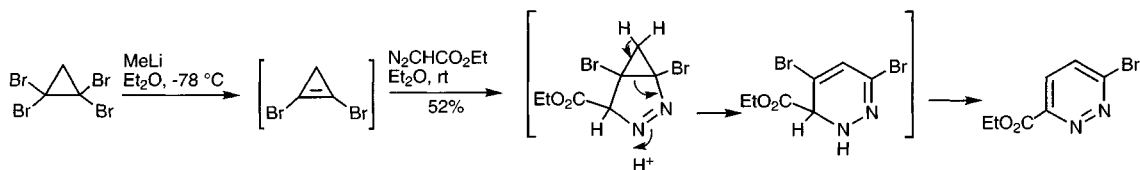
#### 11.14.1.3.2 From thiophene S,S-dioxides

Thiophene *S,S*-dioxides with bulky 3,4-disubstitution undergo Diels-Alder additions with *N*-phenyltriazolinedione to give 1:2 adducts which on hydrolysis are converted into 4,5-disubstituted pyridazines.<sup>160</sup>



#### 11.14.1.3.3 From halocyclopropenes

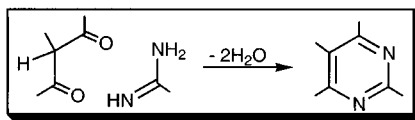
Di, tri-, and tetrahalocyclopropenes undergo cycloaddition with diazoalkanes to give unstable pyrazolines, which readily rearrange to pyridazines with loss of hydrogen halide. Tetrachlorocyclopropene is commercially available but many of the bromo compounds are easily prepared in two steps from vinyl bromides by addition of dibromocarbene, followed by reaction with methyllithium, the last step being carried out *in situ* for the cycloaddition step.<sup>161</sup>



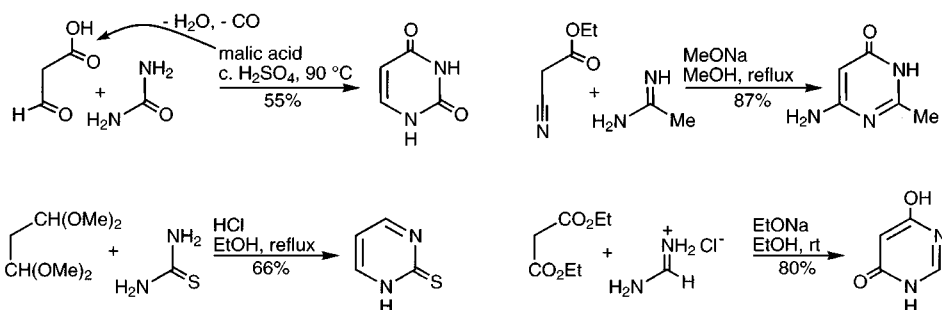
### 11.14.2 Ring synthesis of pyrimidines

#### 11.14.2.1 From a 1,3-dicarbonyl compound and an N-C-N fragment

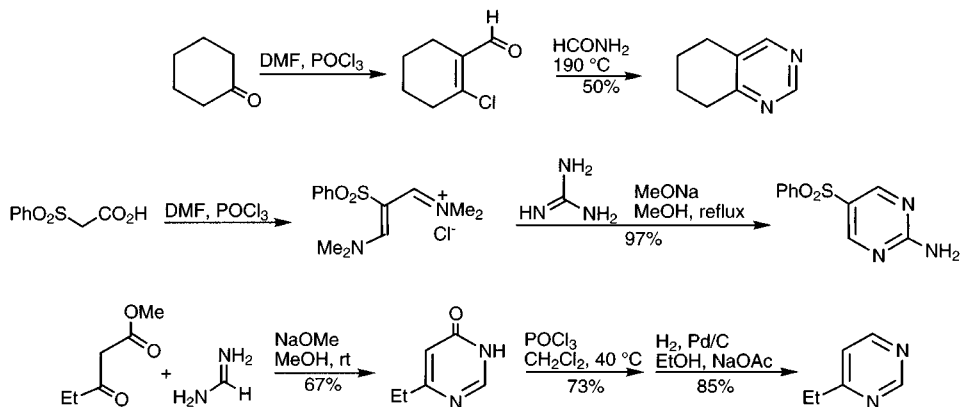
The most general pyrimidine ring synthesis involves the combination of a 1,3-dicarbonyl component with an N-C-N fragment such as a urea, an amidine, or a guanidine.



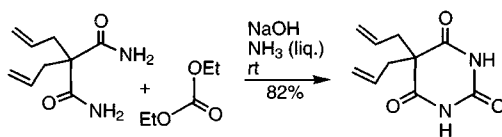
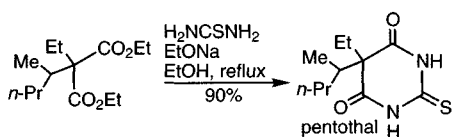
The choice of N–C–N component – amidine,<sup>162</sup> guanidine,<sup>163</sup> or a urea<sup>164</sup> (thiourea<sup>165</sup>) – governs the substitution at C-2 in the product heterocycle. Although not formally ‘N–C–N’ components, formamide,<sup>166</sup> or an orthoester plus ammonia<sup>167</sup> can serve instead in this type of approach. The dicarbonyl component can be generated *in situ*, for example formylacetic acid (by decarboxylation of malic acid), or a synthon used (1,1,3,3-tetramethoxypropane for malondialdehyde), or a nitrile can serve as a carbonyl equivalent, the resulting heterocycle now carrying an amino substituent, as shown in the examples below.<sup>168</sup> The use of 2-bromo-1,1,3,3-tetramethoxypropane provides a route to 5-bromopyrimidine<sup>169</sup> and methanetricarboxaldehyde reacts with amidines to give 5-formylpyrimidines.<sup>170</sup>



Other synthons for 1,3-dicarbonyl compounds which have been successfully applied include  $\beta$ -chloro- $\alpha,\beta$ -unsaturated ketones and aldehydes,<sup>171</sup>  $\beta$ -amino- $\alpha,\beta$ -unsaturated ketones,<sup>172</sup> vinylamidinium salts,<sup>173</sup> and propionic acid, reaction of which with urea gives uracil directly in about 50% yield.<sup>174</sup> 1,3-Ketoesters with formamidine produce 4-pyrimidones.<sup>175</sup> 2-Aminomalondialdehyde leads to 5-aminopyrimidines.<sup>176</sup> In analogy, pyrimidines fused to other rings, for example as in quinazolines, can be made from *ortho*-aminonitriles<sup>177</sup> and in general, from  $\beta$ -enaminoesters.<sup>178</sup>

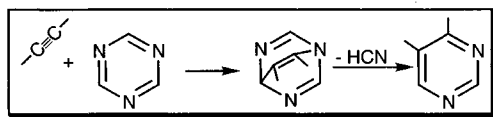


Barbituric acid and barbiturates can be synthesised by reacting a malonate with a urea,<sup>179</sup> or a bis primary amide of a substituted malonic acid with diethyl carbonate.<sup>180</sup>

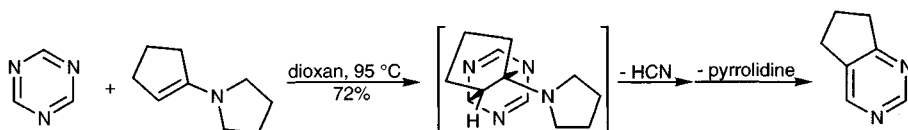


#### 11.14.2.2 By cycloaddition of a 1,3,5-triazine with an alkyne

Cycloaddition of a 1,3,5-triazine with an alkyne (or its equivalent) gives pyrimidines after loss of hydrogen cyanide.

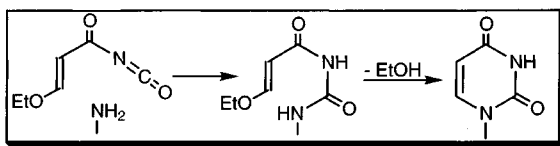


The formation of pyrimidines<sup>181</sup> *via* aza-Diels-Alder reactions is similar to the preparation of pyridazines from tetrazines (see also section 25.2.1).

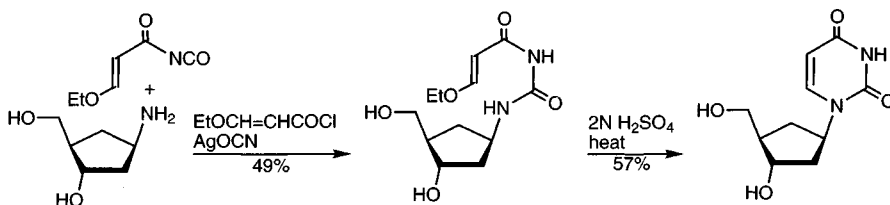


#### 11.14.2.3 From 3-ethoxyacryloyl isocyanate and primary amines

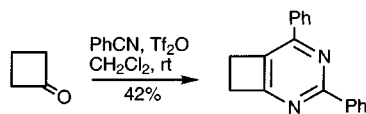
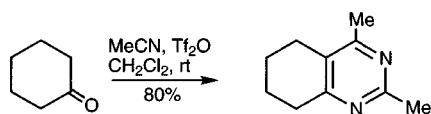
Primary amines add to the isocyanate group in 3-ethoxyacryloyl isocyanate; ring closure then gives pyrimidines *via* intramolecular displacement of the ethoxy group.



Uracils can be prepared *via* reaction of primary amines with 3-ethoxyacryloyl isocyanate;<sup>182</sup> this method is particularly suitable for complex amines and has found much use in recent years in the synthesis of, for example, carbocyclic nucleoside analogues as potential anti-viral agents.<sup>183</sup> The immediate product of amine/isocyanate interaction can be cyclised under either acidic or basic conditions and the method can also be applied to thiouracil synthesis.



Condensation of ketones with two mol equivalents of a nitrile in the presence of trifluoromethanesulfonic acid anhydride is a useful method for the production of a limited range of pyrimidines, where the substituents at C-2 and C-4 are identical.<sup>184</sup>

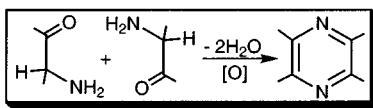


### 11.14.3 Ring synthesis of pyrazines

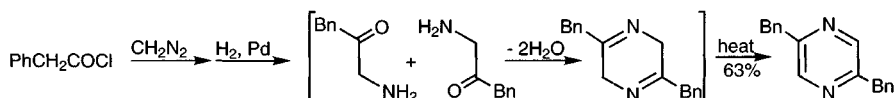
Pyrazine is not easily made in the laboratory. Commercially, the high temperature cyclodehydrogenation of precursors such as *N*-hydroxyethyl ethane-1,2-diamine is used.

#### 11.14.3.1 From the self condensation of a 2-aminoketone

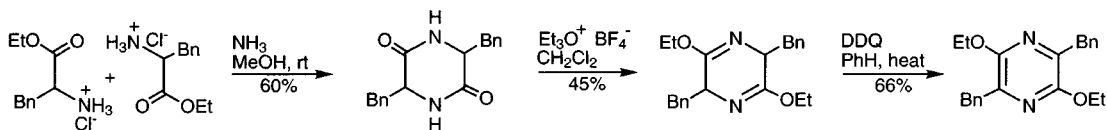
Symmetrical pyrazines result from the spontaneous self condensation of two mol equivalents of a 2-aminoketone, or 2-aminoaldehyde, followed by an oxidation.



2-Amino-carbonyl compounds, which are stable only as their salts, are usually prepared *in situ* by the reduction of 2-diazo-, -oximino- or -azido-ketones. The dihydropyrazines produced by this strategy are very easily aromatised, for example by air oxidation, and often distillation alone is sufficient to bring about disproportionation.<sup>185</sup>

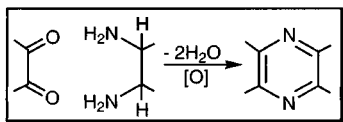


$\alpha$ -Amino-esters are more stable than  $\alpha$ -amino-ketones but nonetheless easily self-condense to give heterocycles, known as 2,5-diketopiperazines. These compounds are resistant to oxidation but can be used to prepare aromatic pyrazines after first converting them into dichloro- or dialkoxy-dihydropyrazines.<sup>186</sup>

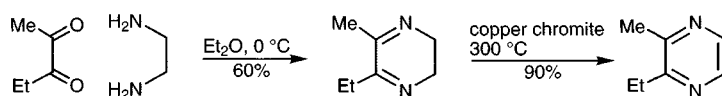


#### 11.14.3.2 From 1,2-dicarbonyl compounds and 1,2-diamines

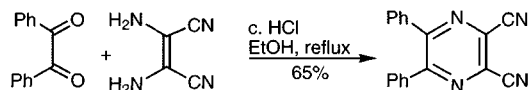
1,2-Dicarbonyl compounds undergo double condensation with 1,2-diamines; an oxidation is then required.



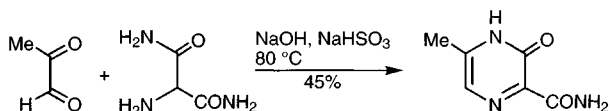
This method is well suited to the formation of symmetrical pyrazines,<sup>187</sup> if both diketone and diamine are unsymmetrical, two isomeric pyrazines are formed.



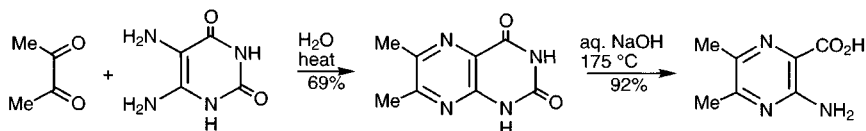
The direct synthesis of aromatic pyrazines along these lines requires a 1,2-diaminoalkene but simple examples of such compounds are not known, however diaminomaleonitrile<sup>188</sup> is stable and serves in this context.



Other dinitrogen components which also carry unsaturation are  $\alpha$ -amino acid amides,<sup>189</sup> from which pyrazinones can be formed; a special example is aminomalonamide and a pyrazinone synthesis using this unit is shown below.<sup>190</sup>

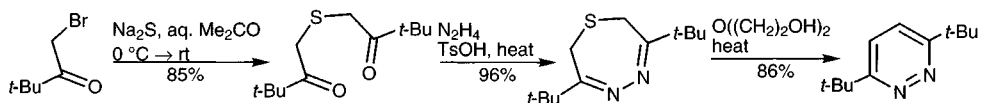


An ingenious modification of the general method uses 5,6-diaminouracil as a masked unsaturated 1,2-diamine: the products can be hydrolysed with cleavage of the pyrimidone ring finally arriving at amino-pyrazine acids as products.<sup>191</sup>



### 11.14.3.3 Pyridazines via sulfides

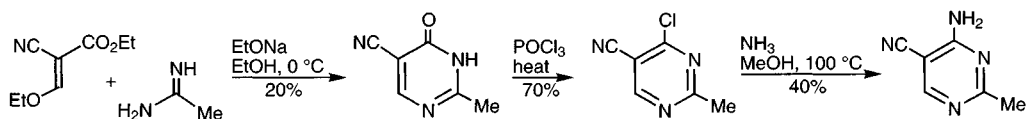
Symmetrically 3,6-disubstituted pyridazines, with a variety of alkyl and aryl substituents, can be constructed *via* ring contraction of a 7-membered sulfide.<sup>192</sup>



## 11.14.4 Notable syntheses of diazines

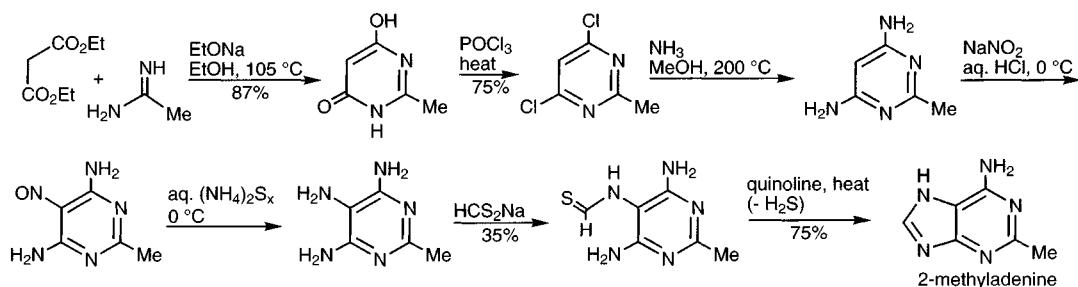
### 11.14.4.1 4-Amino-5-cyano-2-methylpyrimidine

4-Amino-5-cyano-2-methylpyrimidine,<sup>193</sup> is an intermediate used in a synthesis (section 21.14.2.3) of thiamin (vitamin B<sub>1</sub>).



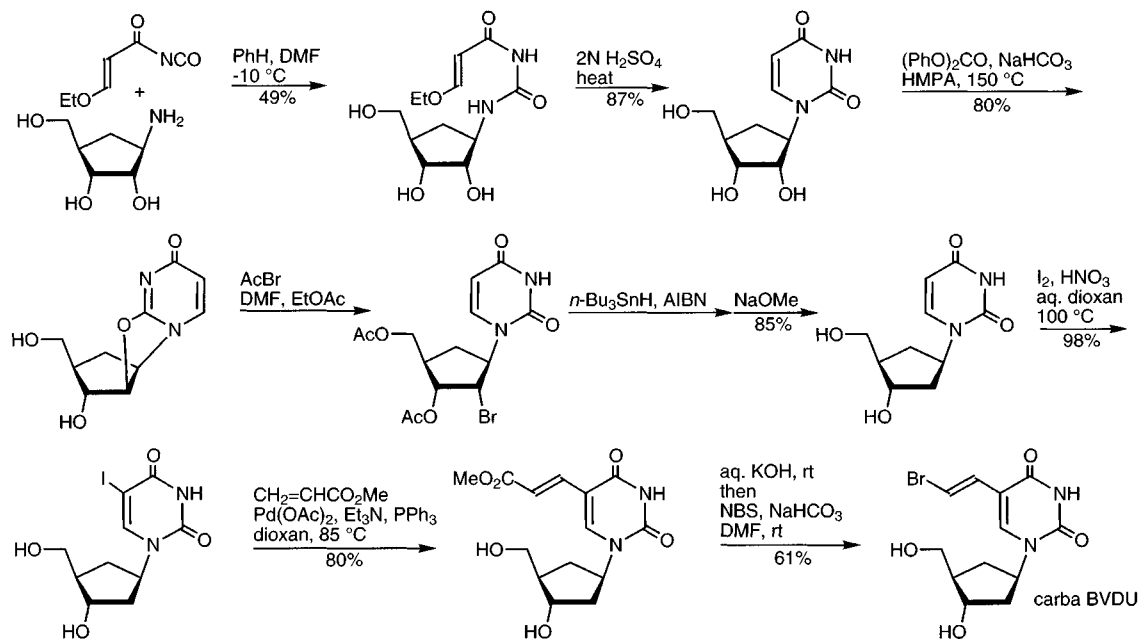
### 11.14.4.2 4,6-Diamino-5-thioformamido-2-methylpyrimidine

4,6-Diamino-5-thioformamido-2-methylpyrimidine can be converted into 2-methyladenine.



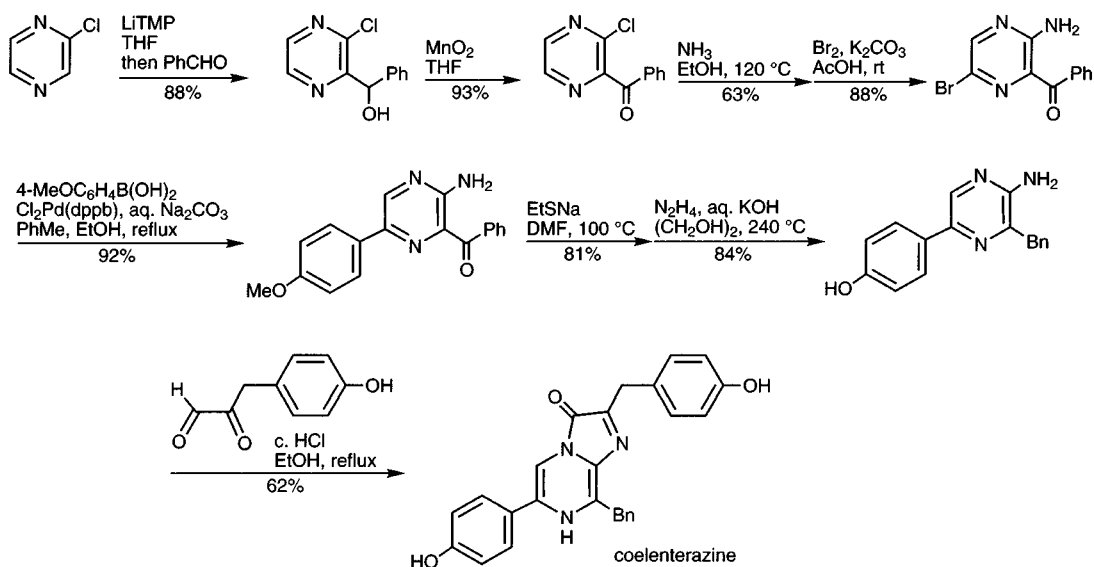
#### 11.14.4.3 Carbocyclic bromovinyldeoxyuridine

Carbocyclic bromovinyldeoxyuridine (CarbaBVDU) is an anti-viral agent.<sup>194</sup>



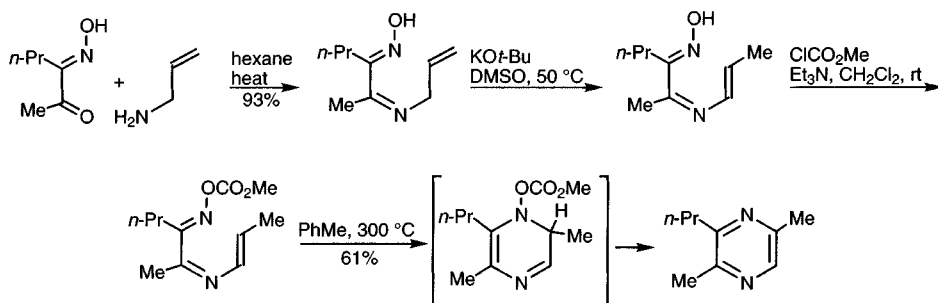
#### 11.14.4.4 Coelenterazine

Coelenterazine, a bioluminescent compound from a jellyfish, with potential for use in bioassays, has been synthesised in an overall 25% yield from chloropyrazine.<sup>195</sup>



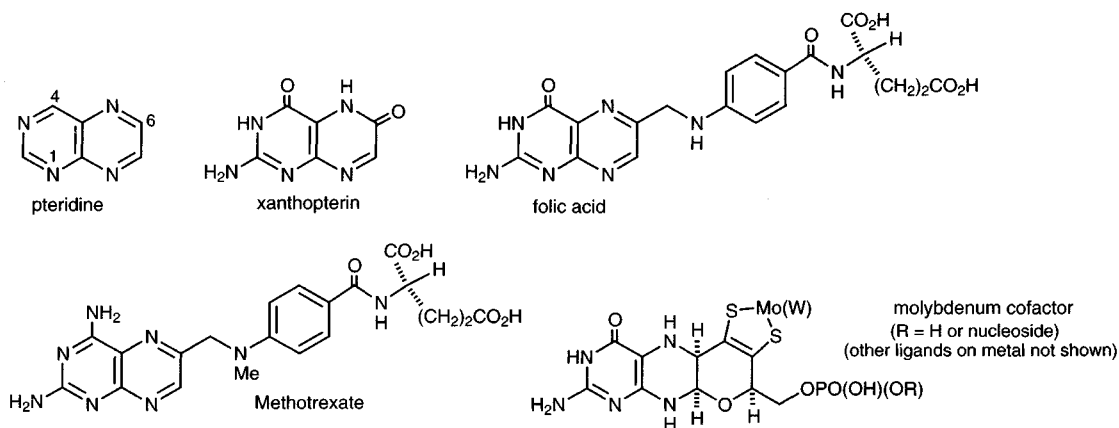
#### 11.14.4.5 2,5-Dimethyl-3-*n*-propylpyrazine

Alkylpyrazines can be produced by an ingenious sequence involving an electrocyclic ring closure of a 1,4-diazatriene, aromatisation being completed by loss of the oxygen from the original oxime hydroxyl group.<sup>196</sup>

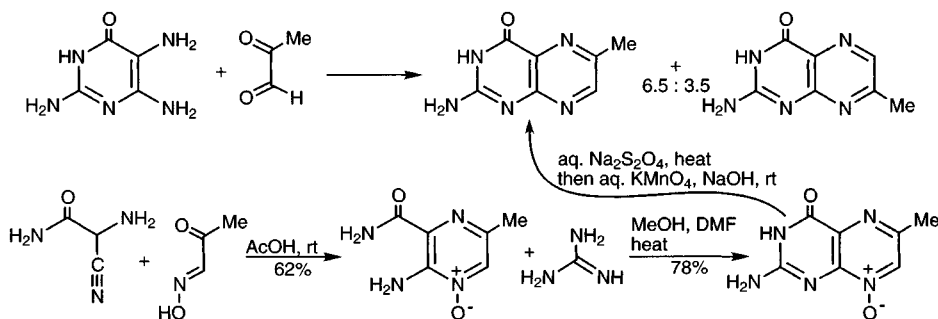


### 11.15 Pteridines

Pyrazino[2,3-*d*]pyrimidines are known as 'pteridines',<sup>197</sup> because the first examples of the ring system, as natural products, were found in pigments, like xanthopterin (yellow), in the wings of butterflies (*Lepidoptera*). The pteridine ring system has subsequently been found in coenzymes which use tetrahydrofolic acid (derived from the vitamin folic acid) and in the cofactor of the oxomolybdoenzymes<sup>198</sup> and comparable tungsten enzymes. It is also present in the anti-cancer drug Methotrexate.



The synthesis of the pteridine ring system has been approached by two obvious routes: one is the fusion of the pyrazine ring onto a preformed 4,5-diaminopyrimidine, and the second, the elaboration of the pyrimidine ring on a preformed pyrazine. The first of these, the *Isay synthesis*, suffers from the disadvantage that condensation of the heterocyclic 1,2-diamine with an unsymmetrical 1,2-dicarbonyl compound usually leads to a mixture of two 5/6-substituted isomers.<sup>199</sup> It was to avoid this difficulty that the alternative strategy, the *Taylor synthesis*, now widely used, starting with a pyrazine, was developed.<sup>200</sup> This approach has the further advantage that because the pyrazine ring is presynthesised, using 2-cyanoglycinamide,<sup>201</sup> it eventually produces, regioselectively, 6-substituted pteridines – substitution at the 6-position is the common pattern in natural pteridines.



## Exercises for chapter 11

### Straightforward revision exercises (consult chapters 10 and 11)

- Why is it difficult to form diprotonic salts from diazines?
- How do uridine, thymidine, and cytidine differ?
- Are the diazines more or less reactive towards *C*-electrophilic substitution than pyridine?
- What factor assists and what factor mediates against nucleophilic displacement of hydrogen in diazines?
- Which is the only chlorodiazine which does not undergo easy nucleophilic displacement, and why?
- What precaution is usually necessary in order to lithiate a diazine?

- (g) Write out one example each where a pyridazine, a pyrimidine and a pyrazine undergo a cycloaddition, acting as a diene or an azadiene.
- (h) How could one convert an oxydiazine, where the oxygen is  $\alpha$  to a nitrogen, (i) into a corresponding chloro-diazine, (ii) efficiently into a corresponding *N*-methylidiazinone, (iii) into a corresponding amino-diazine but without involving a chlorodiazine?
- (i) What is the product from hydrazine and a 1,4-keto-ester? How could it be converted into a pyridazinone?
- (j) Given pentane-2,4-dione how could one prepare (i) 4,6-dimethylpyrimidine, (ii) 4,6-dimethyl-2-pyrimidone, (iii) 2-amino-4,6-dimethylpyrimidine?
- (k) What substitution pattern is the easiest to achieve in the ring synthesis of pyrazines?

### More advanced exercises

1. What compounds are produced at each stage in the following sequences: (i) pyridazin-3-one reacted with  $\text{POCl}_3$  ( $\rightarrow \text{C}_4\text{H}_3\text{N}_2\text{Cl}$ ) and this with  $\text{NaOMe}$  ( $\rightarrow \text{C}_5\text{H}_6\text{N}_2\text{O}$ ); (ii) chloropyrazine with  $\text{BuNH}_2/120^\circ\text{C}$  ( $\rightarrow \text{C}_8\text{H}_{13}\text{N}_3$ )?
2. What are the structures of the compounds formed: (i)  $\text{C}_6\text{H}_9\text{IN}_2\text{S}$  from 3-methylthiopyridazine and  $\text{C}_6\text{H}_8\text{ClIN}_2$  from 3-chloro-6-methylpyridazine, each with  $\text{MeI}$ ; (ii)  $\text{C}_5\text{H}_2\text{Cl}_2\text{N}_2\text{O}$  from treatment of 2,6-dichloropyrazine with  $\text{LiTMP}$  then  $\text{HCO}_2\text{Et}$ ; (iii)  $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$  from 2,6-dimethoxypyrazine with  $\text{LiTMP}$ , then  $\text{I}_2$  then  $\text{PhC}\equiv\text{CH}/\text{Pd}(0)$ ; (iv)  $\text{C}_6\text{H}_9\text{N}_3$  from 2-aminopyrimidine first with  $\text{NaNO}_2/\text{c. HCl}/-15^\circ\text{C}$  (and then the product with  $\text{Me}_2\text{NH}$ ); (v)  $\text{C}_{18}\text{H}_{14}\text{N}_2$  from 3-methyl-6-phenylpyridazine with  $\text{PhCH}=\text{O}/\text{Ac}_2\text{O}/\text{heat}$ ?
3. Write sequences and structures for intermediates and final products in the following ring syntheses: (i) chlorobenzene with succinic anhydride/ $\text{AlCl}_3$  ( $\rightarrow \text{C}_{10}\text{H}_9\text{ClO}_3$ ), then this with  $\text{N}_2\text{H}_4$  ( $\rightarrow \text{C}_{10}\text{H}_9\text{ClN}_2\text{O}$ ) and finally this with  $\text{Br}_2/\text{AcOH}$  ( $\rightarrow \text{C}_{10}\text{H}_7\text{ClN}_2\text{O}$ ); (ii) 2,5-dimethylfuran reacted with  $\text{Br}_2$  in  $\text{MeOH}$  ( $\rightarrow \text{C}_8\text{H}_{14}\text{O}_3$ ) then this firstly with aqueous acid and then hydrazine ( $\rightarrow \text{C}_6\text{H}_8\text{N}_2$ ); (iii) 1,1-dimethoxybutan-3-one with guanidinium hydrogen carbonate ( $\rightarrow \text{C}_5\text{H}_7\text{N}_3$ ); (iv) ethyl cyanoacetate with guanidine/ $\text{NaOEt}$  ( $\rightarrow \text{C}_4\text{H}_6\text{N}_4\text{O}$ ); (v) ethyl cyanoacetate with urea/ $\text{EtONa}$  ( $\rightarrow \text{C}_4\text{H}_5\text{N}_3\text{O}_2$ ); (vi)  $(\text{EtO})_2\text{CHCH}_2\text{CH}(\text{OEt})_2/\text{HCl}/\text{urea}$  ( $\rightarrow \text{C}_4\text{H}_4\text{N}_2\text{O}$ ); (vii)  $\text{MeOCH}_2\text{COMe}$  with  $\text{EtO}_2\text{CH}/\text{Na}$  ( $\rightarrow \text{C}_5\text{H}_8\text{O}_3$ ), then this with thiourea ( $\rightarrow \text{C}_6\text{H}_8\text{N}_2\text{OS}$ ), then this with  $\text{H}_2/\text{Ni}$  ( $\rightarrow \text{C}_6\text{H}_8\text{N}_2\text{O}$ ); (viii)  $\text{PhCOCH}_2\text{CO}_2\text{Et}$  with  $\text{EtC}(=\text{NH})\text{NH}_2$  ( $\rightarrow \text{C}_{12}\text{H}_{12}\text{N}_2\text{O}$ ); (ix)  $\text{PhCOCHO}$  with  $\text{MeCH}(\text{NH}_2)\text{CONH}_2$  ( $\rightarrow \text{C}_{11}\text{H}_{10}\text{N}_2\text{O}$ ).

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