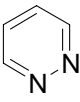
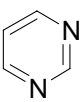
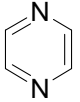
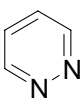
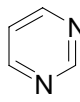
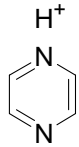
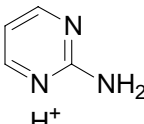
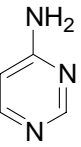
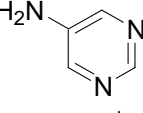
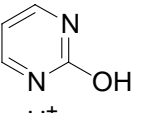
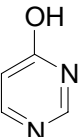


## Six-Membered Ring Systems with two or more heteroatoms

### 7.5. General aspects of the chemistry of diazines, triazines and tetrazines

Table 7.5.1. pKa values (aqueous solution, 20°C) of some citations derived from diazines

 H <sup>+</sup> 2.24	 H <sup>+</sup> 1.23	 H <sup>+</sup> 0.51	 H <sup>+</sup> -7.1	 H <sup>+</sup> -6.3	 H <sup>+</sup> -6.6
 H <sup>+</sup> 3.54	 H <sup>+</sup> 5.69	 H <sup>+</sup> 2.83	 H <sup>+</sup> 2.15	 H <sup>+</sup> 1.66	

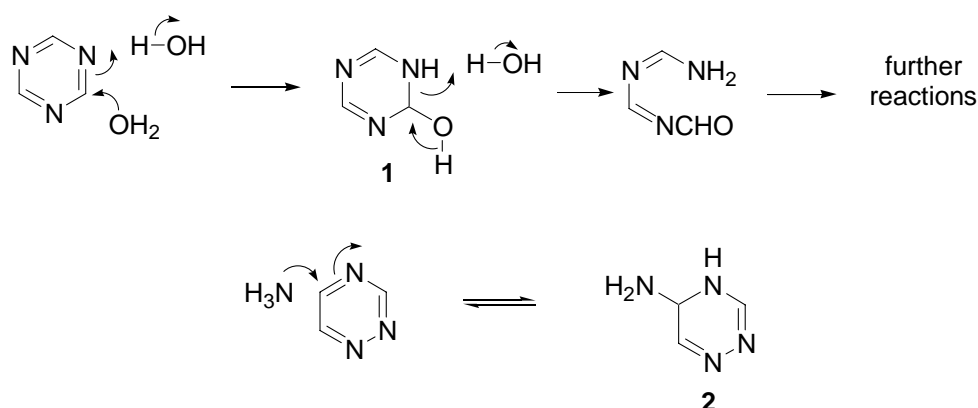
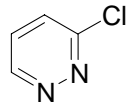
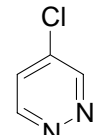
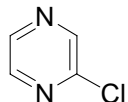
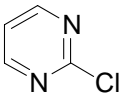
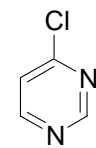
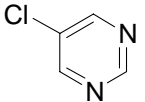


Figure 7.5.2. Examples of nucleophilic addition to 1,3,5-triazines and 1,2,4-triazines

Table 7.5.2. Relative rates of nucleophilic displacement of chloride by 4-nitrophenoxide (4-NO<sub>2</sub>PhOH, MeOH, 50°C)

 $1.2 \times 10^{14}$	 $1.9 \times 10^{14}$	 $4.1 \times 10^{14}$
 $6.3 \times 10^{16}$	 $1.1 \times 10^{15}$	 $1.2 \times 10^{13}$

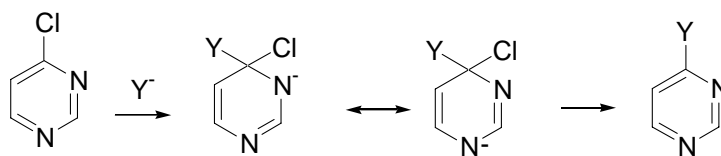


Figure 7.5.3. Nucleophilic displacement in 4-chloropyrimidine.

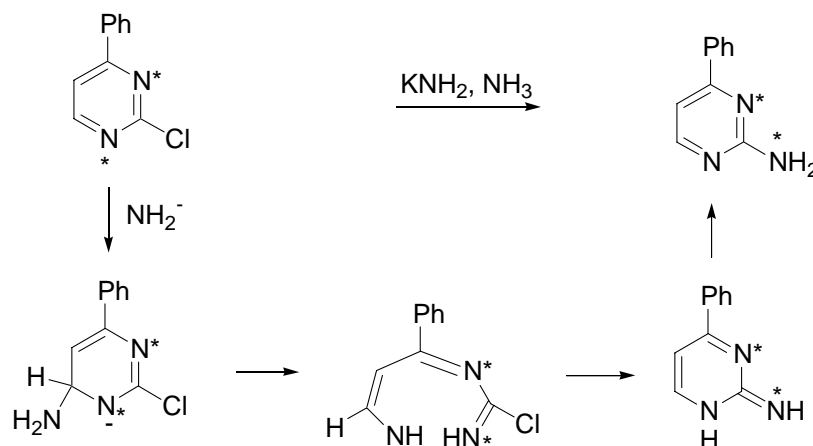
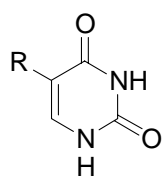


Figure 7.5.4. Substitution by the  $S_N$ (ANRORC) mechanism.

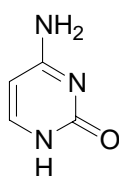
(ANARORC = **A**ddition of **N**ucleophile, **R**ing **O**pening and **R**ing **C**losure)

## 7.6. Pyrimidines and purines

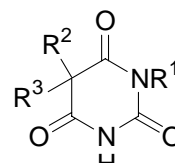
### 7.6.1. Introduction



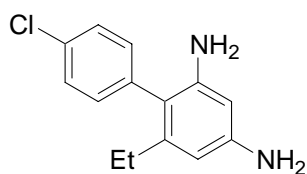
**3a:** R = H  
**3b:** R = Me  
**3c:** R = F



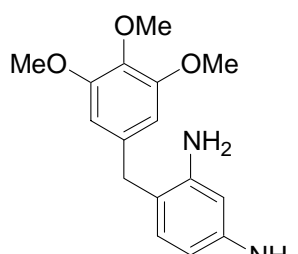
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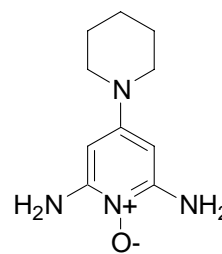
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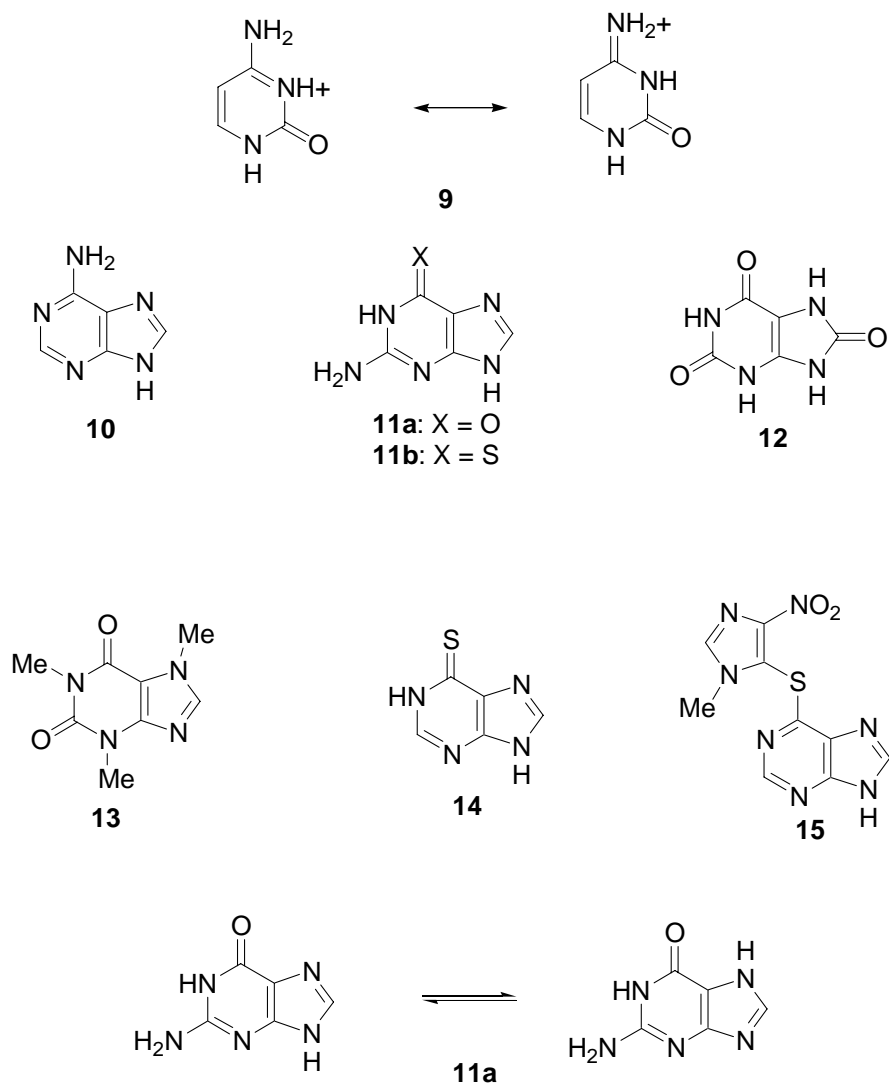
**6**



**7**



**8**



### 7.6.2. Synthesis of pyrimidines

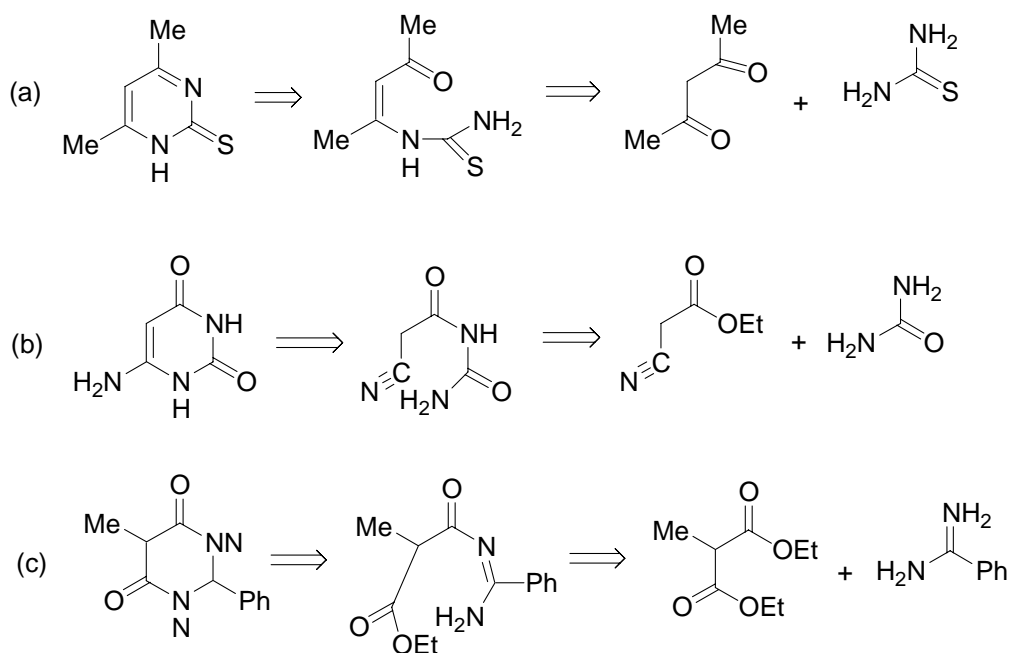


Figure 7.6.5. Analysis of routes to pyrimidines.

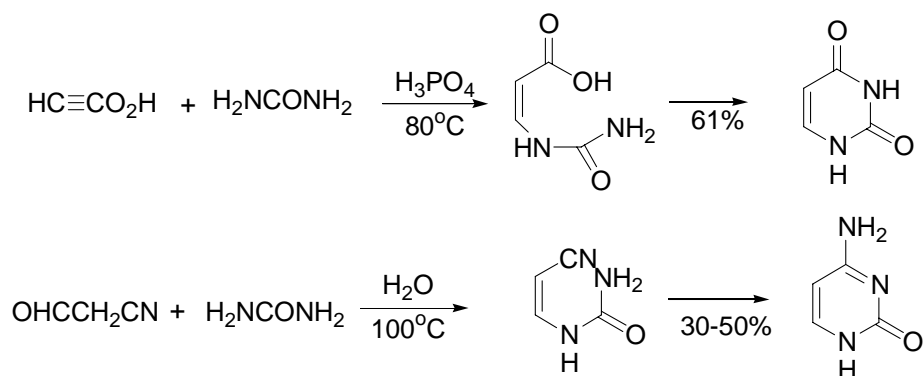


Figure. 7.6.6. Routes to uracil and cytosine.

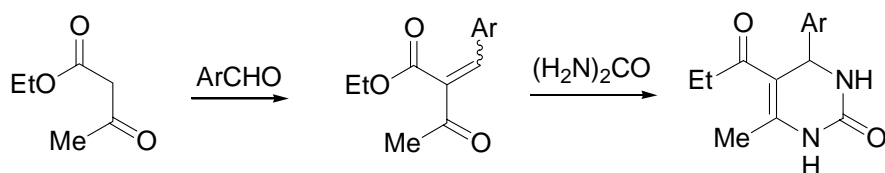


Figure. 7.6.7. The classical Biginelli dihydropyrimidine synthesis.

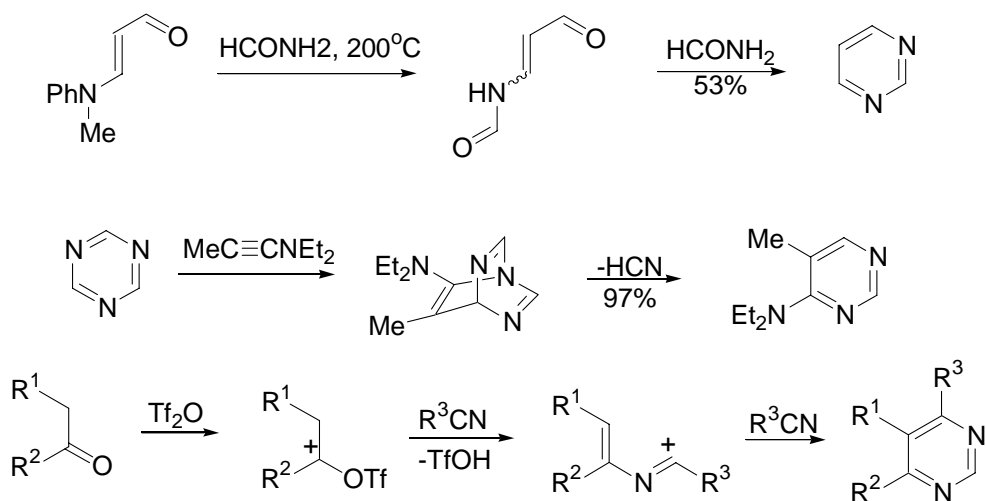


Figure 7.6.8. Some other routes to pyrimidines.

### 7.6.3. Synthesis of purines

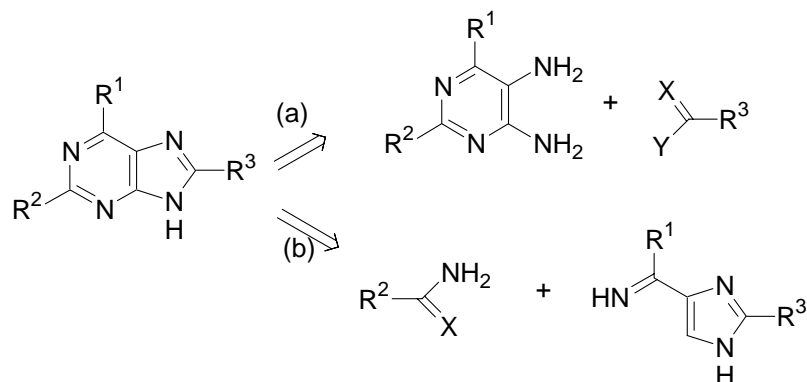


Figure 7.6.9. Analysis of two routes to purines.

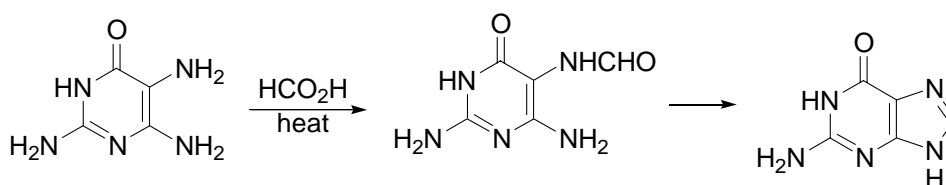


Figure 7.6.10. The Traube synthesis of guanine.

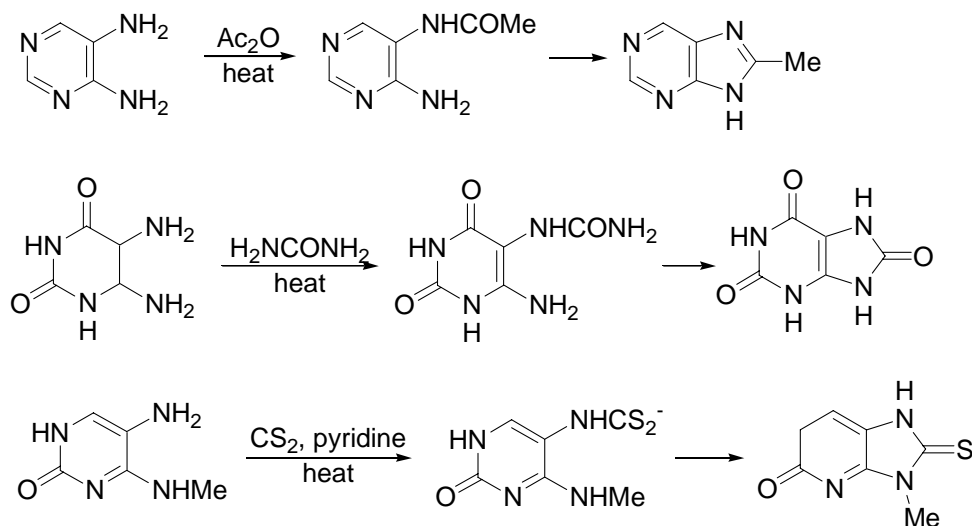


Figure 7.6.11. Examples of purine synthesis from pyrimidines.

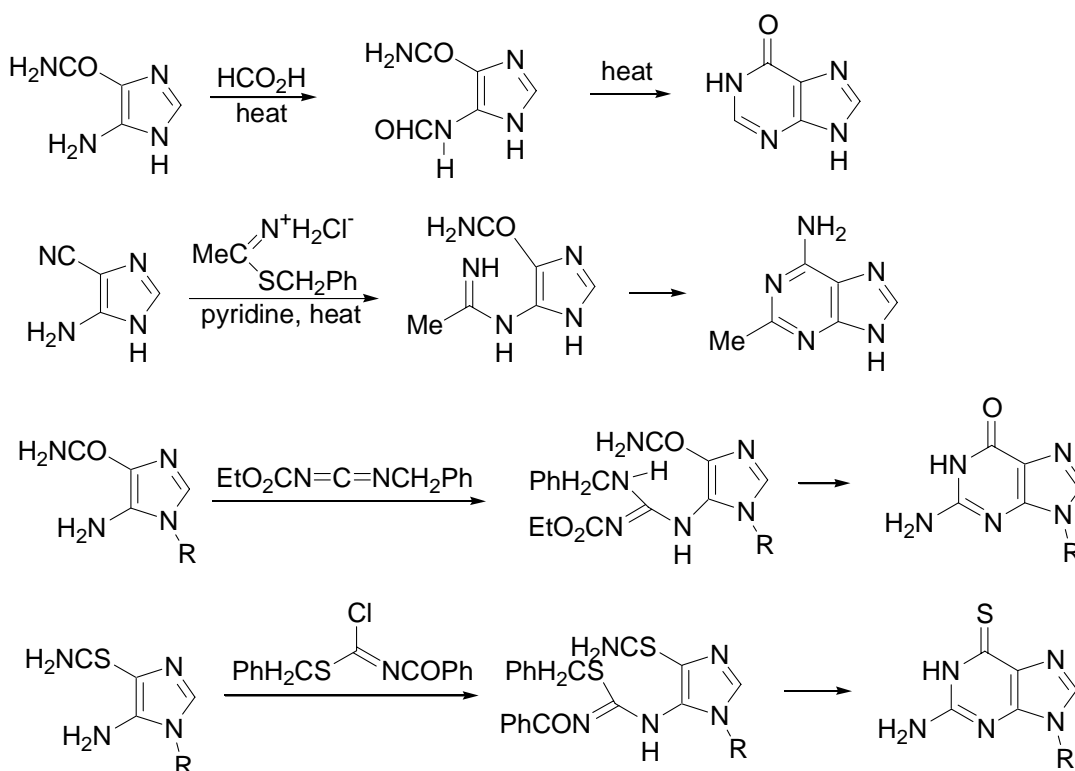


Figure 7.6.12. Examples of purine synthesis from imidazoles.

## 7.6.4 Reactions of pyrimidines

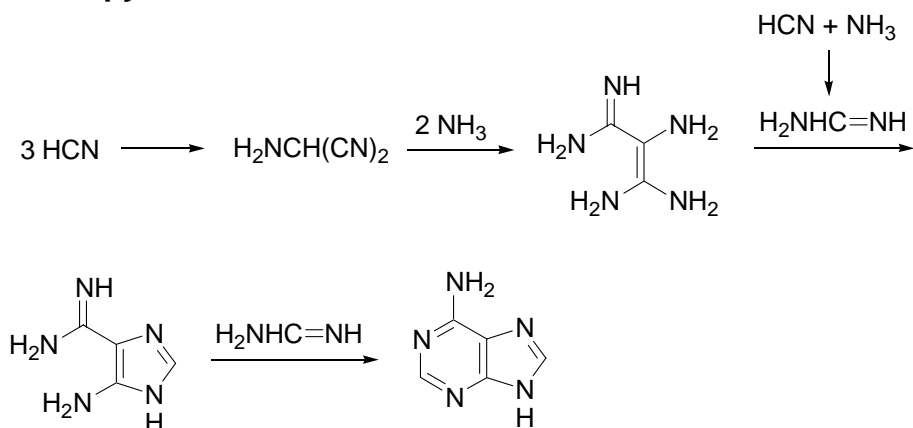


Figure 7.6.13. A route to adenine from hydrogen cyanide.

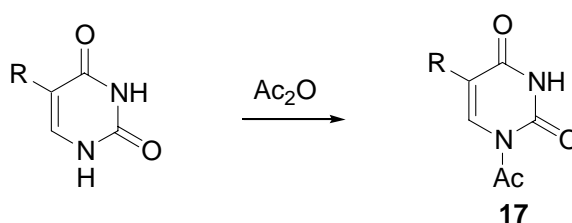


Figure 7.6.14. Acetylation of uracil and thymine.

Table 7.6.3. Electrophile substitution of uracil

Electrophile	Reagents and conditions	Yield (%)
$\text{NO}_2^+$	$\text{HNO}_3$ (d. 1.5), $75^\circ\text{C}$	80
$\text{Br}^+$	$\text{Br}_2$ , $\text{H}_2\text{O}$ , $100^\circ\text{C}$	90
$\text{Cl}^+$	$\text{NCS}$ , $\text{AcOH}$ , $50^\circ\text{C}$	52
$\text{F}^+$	$\text{F}_2$ , $\text{AcOH}$ , $10^\circ\text{C}$	92
$\text{SO}_2\text{Cl}^+$	$\text{ClSO}_3\text{H}$ , $40\text{-}100^\circ\text{C}$	-
$\text{CH}_2=\text{NMe}_2^+$	$(\text{CH}_2\text{O})_n$ , $\text{Me}_2\text{NH}$ , $78^\circ\text{C}$	76
$\text{CH}_2\text{Cl}^+$	$(\text{CH}_2\text{O})_n$ , $\text{HCl}$ , $80^\circ\text{C}$	57
$\text{CH}_2\text{OH}^+$	$\text{CH}_2\text{O}$ aq., rt	-

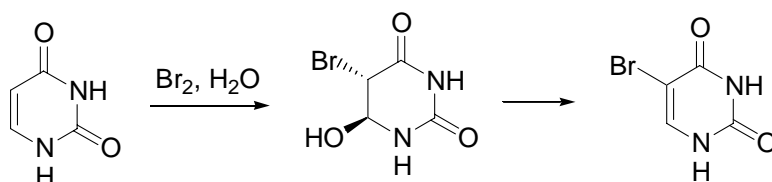


Figure 7.6.15. Bromination of uracil.

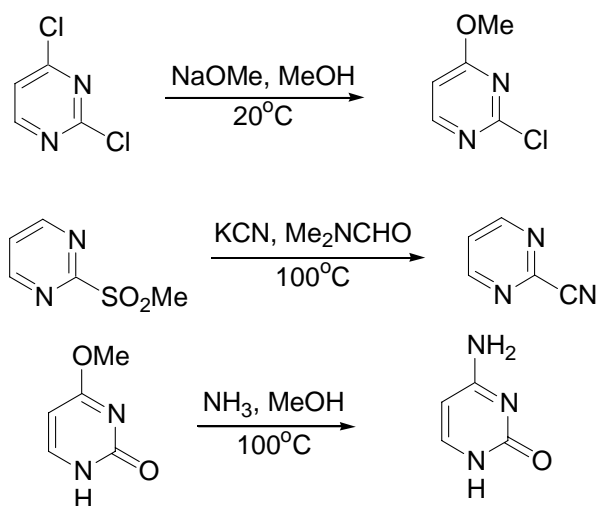


Figure 7.6.16. Examples of nucleophilic displacement.

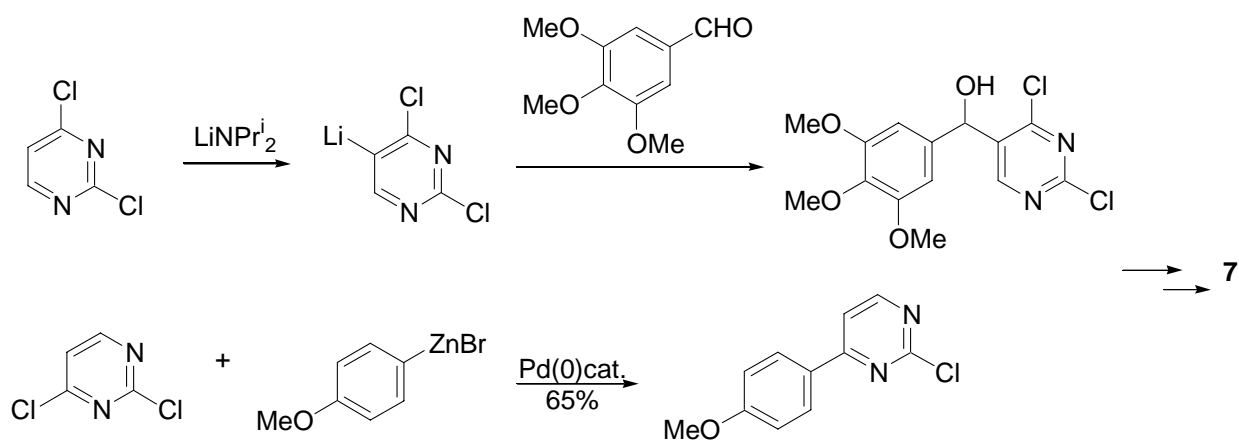


Figure 7.6.17. Substitution of pyrimidines by directed lithiation and by palladium(0) coupling.

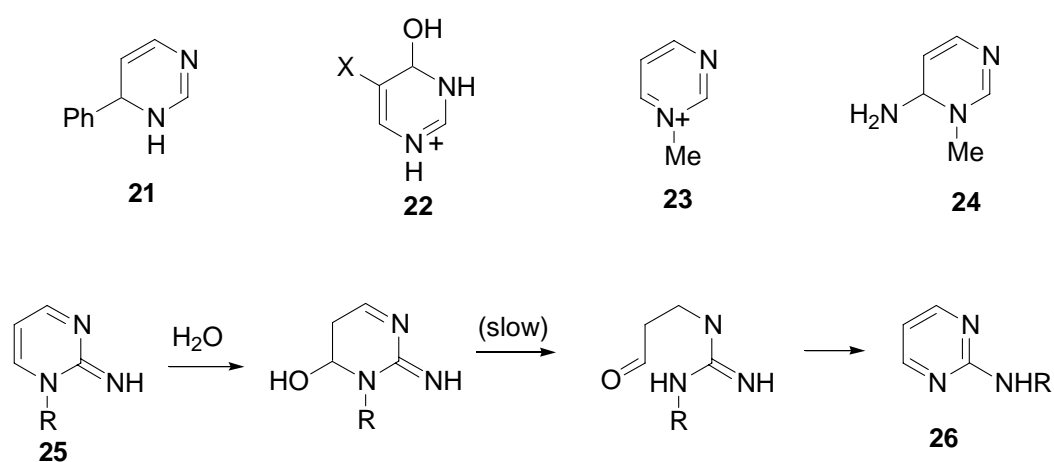
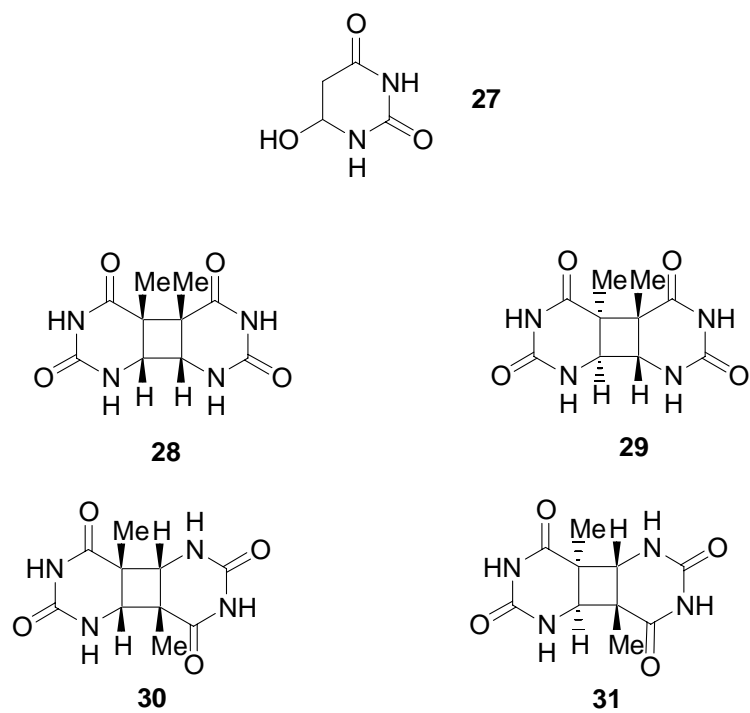


Figure 7.6.18. The Dimroth rearrangement.



### 7.6.5 Reactions of purines

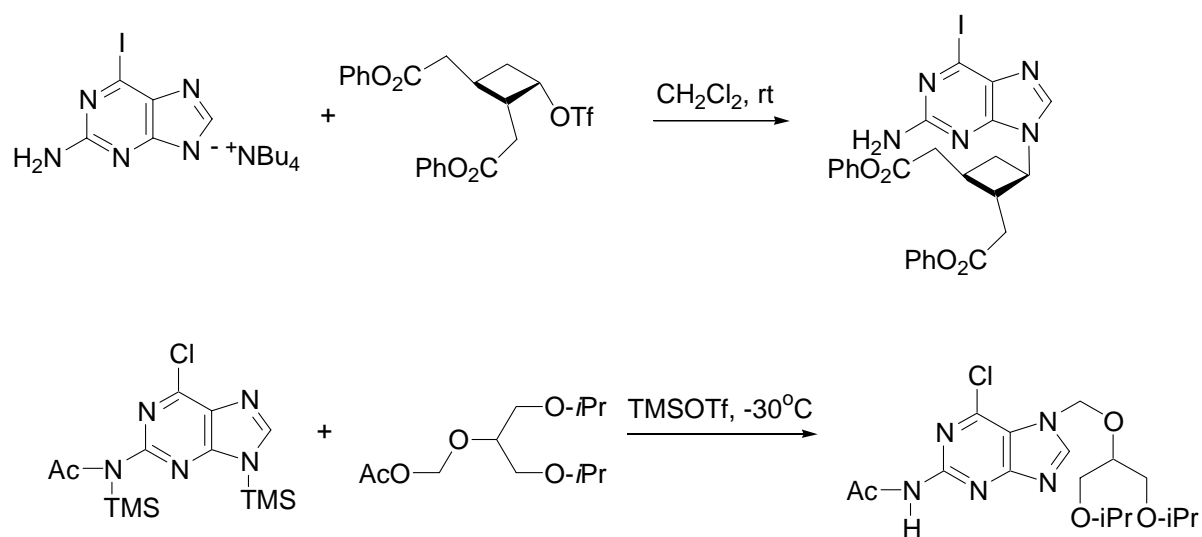


Figure 7.6.19 Examples of selective alkylation at N-9 and N-7



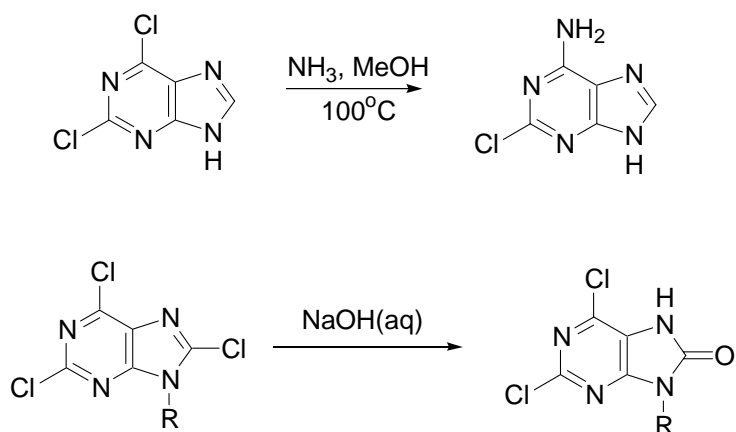


Figure 7.6.20 Examples of selective displacement of chloride.

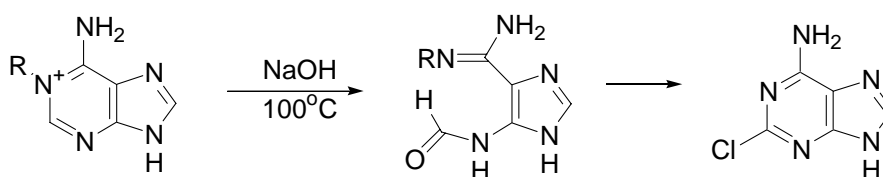


Figure 7.6.21 Dimroth rearrangement of an alkylated adenine.

## 7.6.6 Pyrimidines and purines in nucleic acids

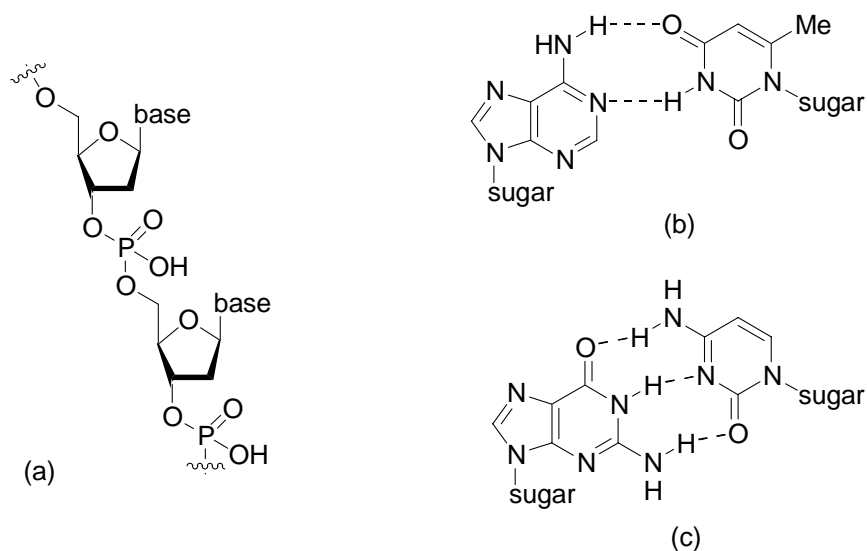
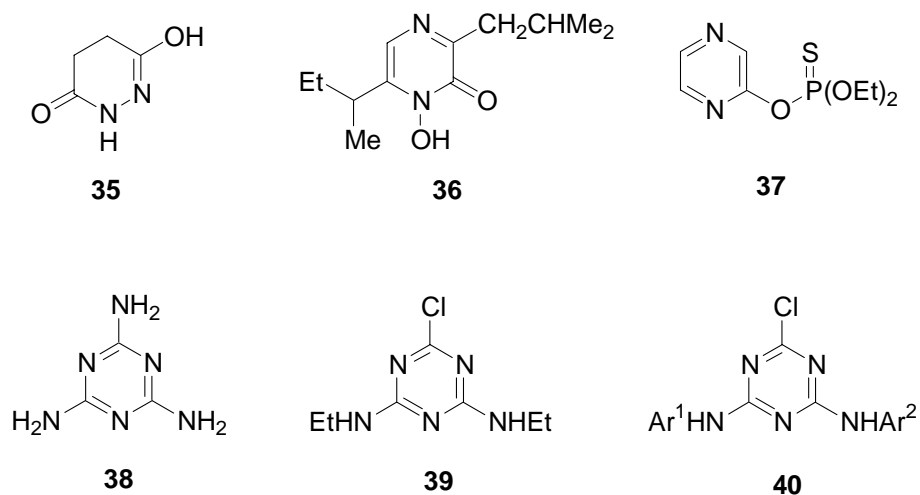


Figure 7.6.22 (a) Two of the repeating units in the primary structure of DNA; (b) adenine-thymine pairing; (c) guanine-cytosine pairing.

## 7.7 Other diazines, triazines and tetrazines

### 7.7.1. Introduction



### 7.7.2. Methods of ring synthesis

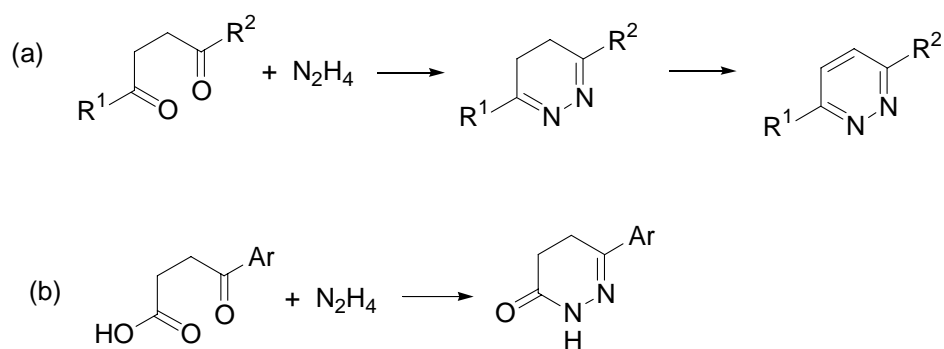


Figure 7.6.23 Routes to the pyridazine ring system.

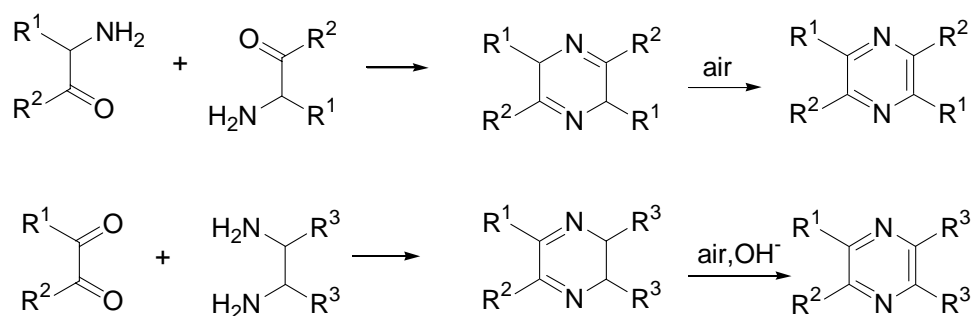


Figure 7.6.24 General routes to pyrazines

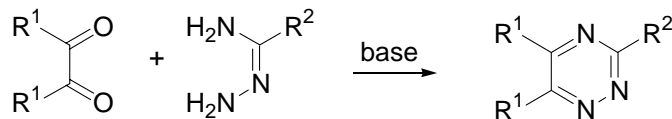
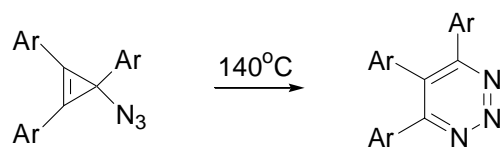


Figure 7.6.25. Routes to 1,2,3- and 1,2,4-triazines.

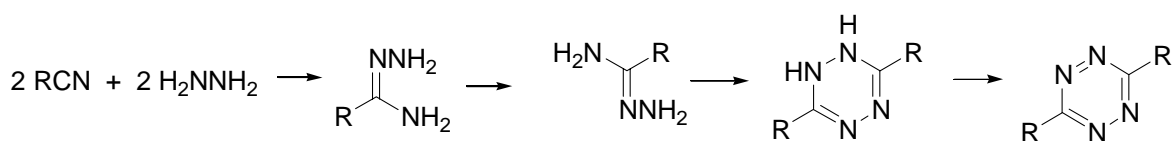


Figure 7.6.26. A route to 1,2,4,5-tetrazines.

### 7.7.3. Chemical properties

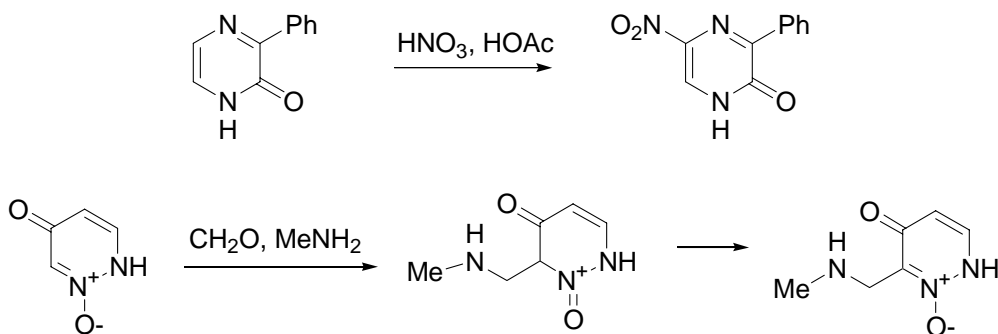


Figure 7.6.27. Examples of electrophilic substitution.

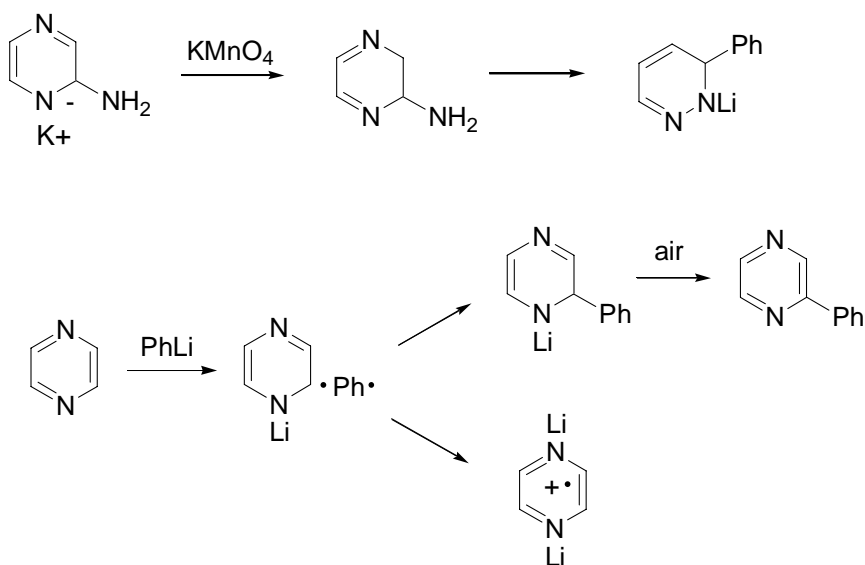
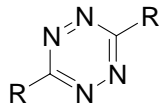
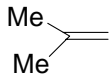
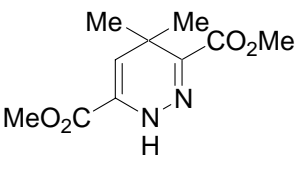
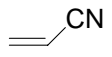
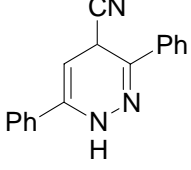
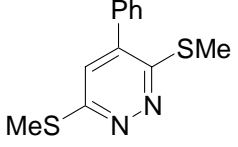
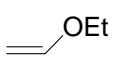
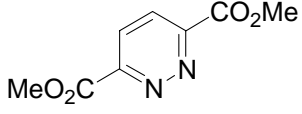

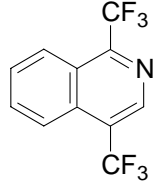


Figure 7.6.28. The reaction of pyrazine with phenyllithium.

Table 7.5 Diels-Alder reactions of 1,2,4,5-tetrazines

R in 	Dienophile, conditions	Product
(i) CO <sub>2</sub> Me	 CH <sub>2</sub> Cl <sub>2</sub> , 25°C	
(ii) Ph	 100°C/5 days	
(ii) SMe	PhC≡CH 166°C/12 h	
(iv) CO <sub>2</sub> Me	 , dioxane, 25°C	
(v) CF <sub>3</sub>	 140°C/24 h	

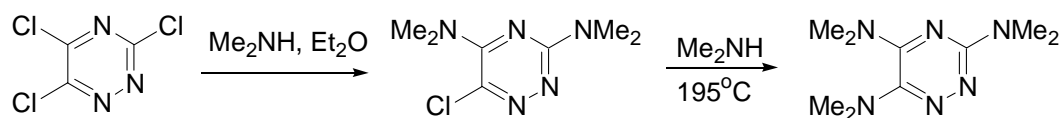
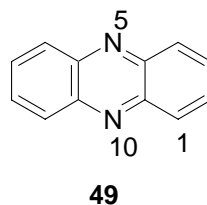
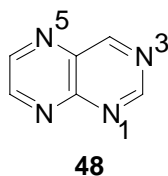
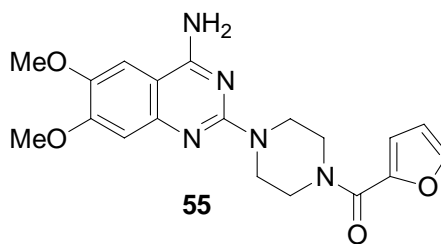
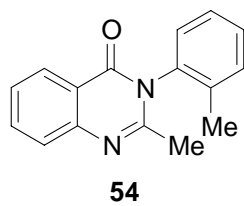
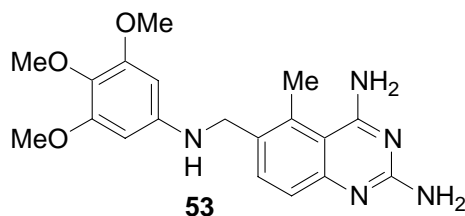
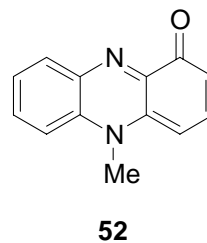
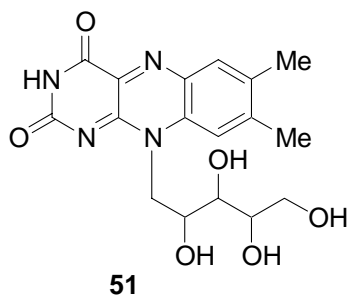
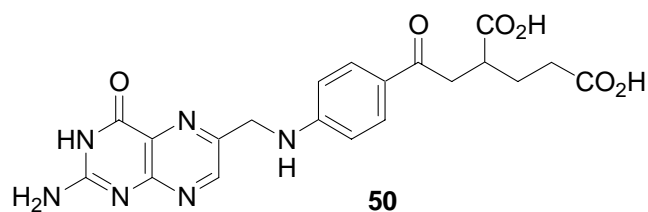


Figure 7.6.29. Sequential displacement of chloride from trichloro-1,2,4-triazine.

## 7.7. Some fused ring systems

### 7.7.1 Introduction





### 7.7.2 Ring synthesis

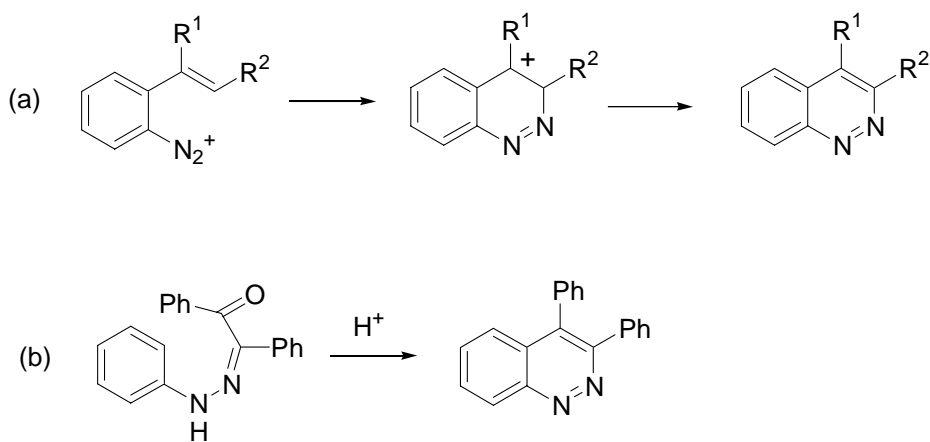


Figure 7.6.30. Routes to cinnolines

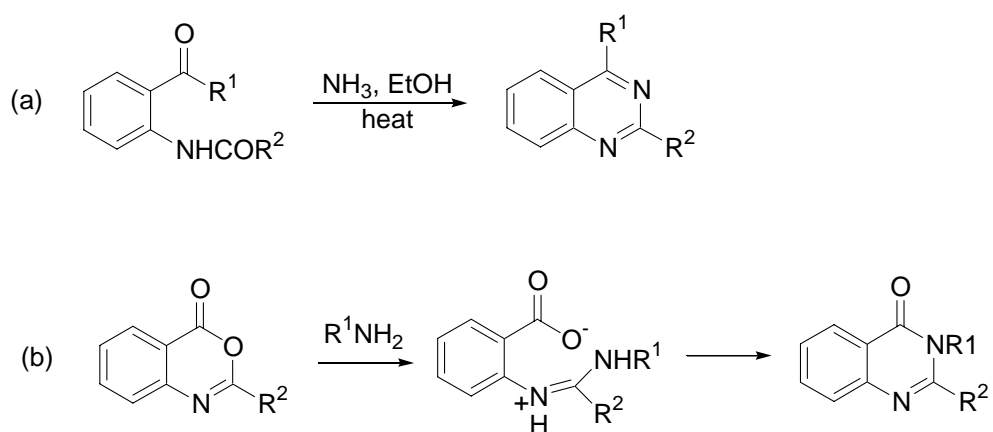


Figure 7.6.31. Routes to quinazolines.

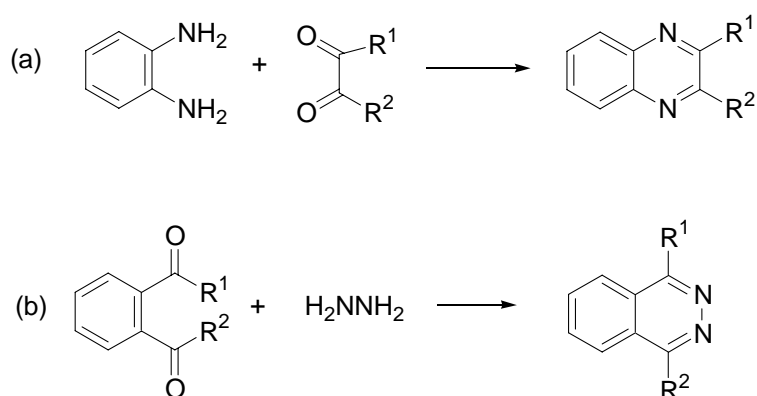


Figure 7.6.32. Routes to quinoxalines and phthalazines.

### 7.7.3 Chemical properties

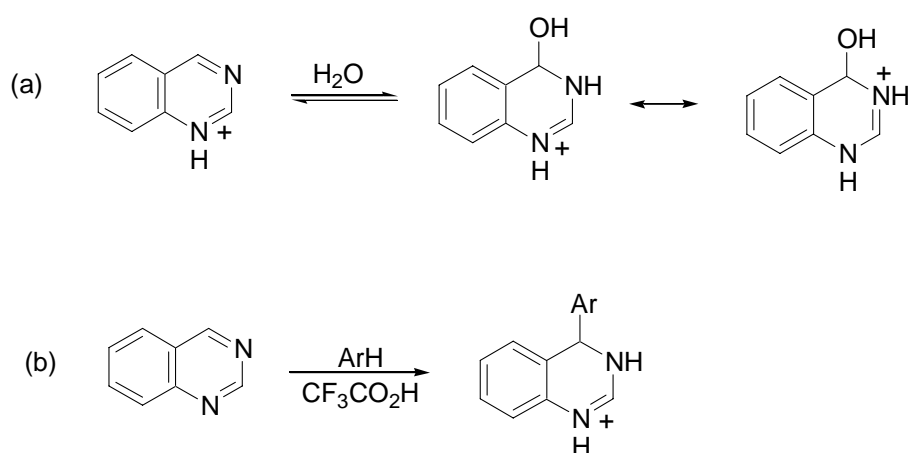


Figure 7.6.33. Addition reaction of 1-quinazolinium cations.

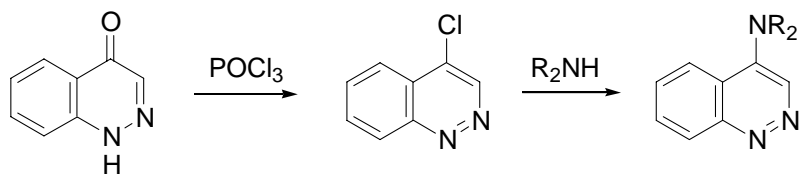
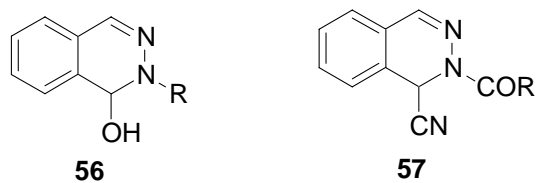


Figure 7.6.34. Formation and reaction of 4-chlorocinnoline.

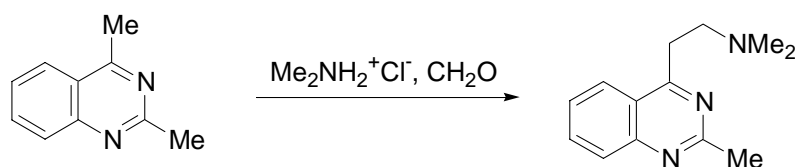
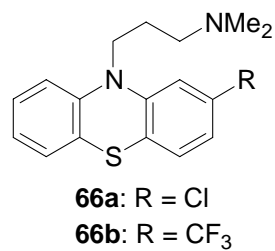
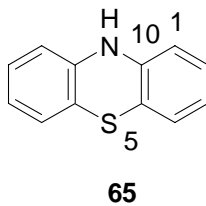
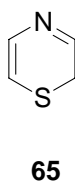
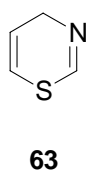
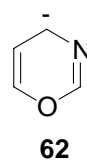
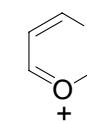
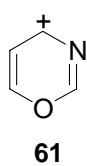
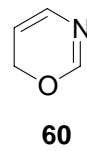
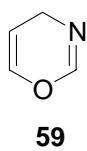
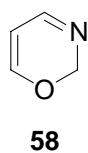


Figure 7.6.35. Mannich reaction of 2,4-dimethylquinazoline.

## 7.8 Oxazines and thiazines

### 7.8.1 Introduction



### 7.8.2 1,3-Oxazines

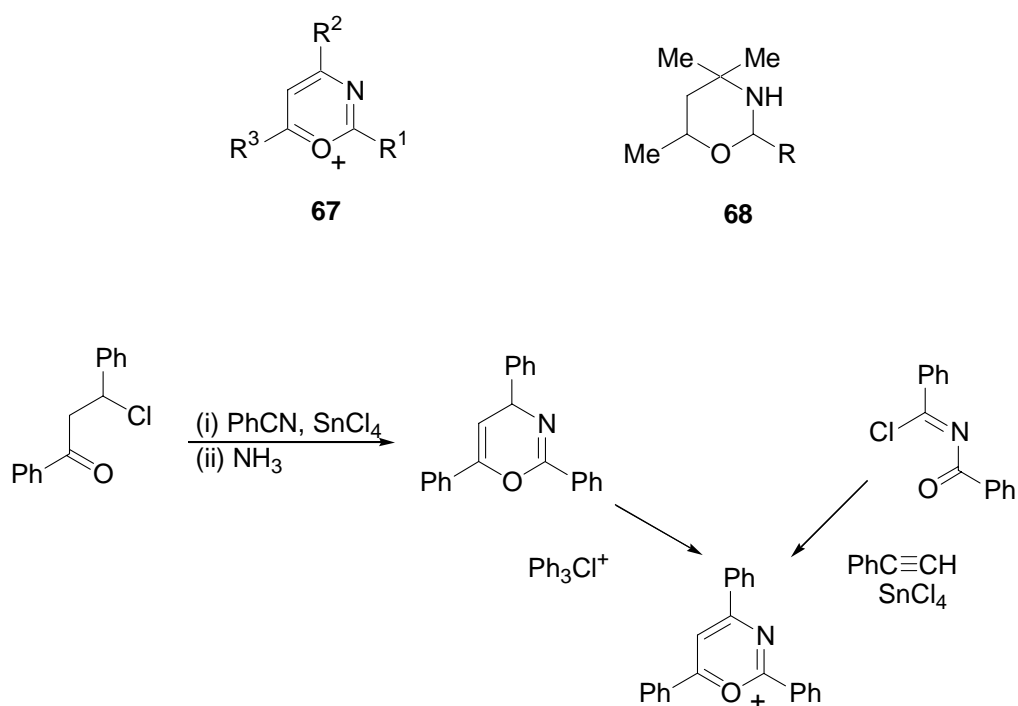


Figure 7.6.36. Routes to 2,4,6-triphenyloxazinium salts.

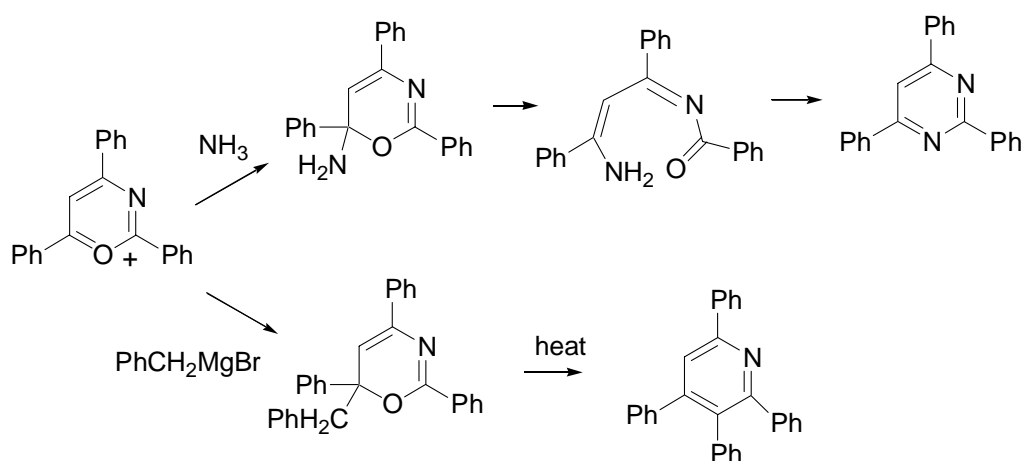


Figure 7.6.37. Reactions with nucleophiles.

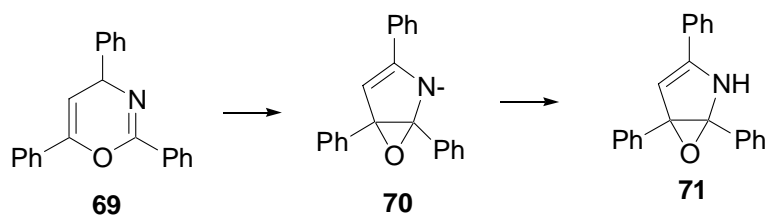


Figure 7.6.38. Ring contraction of the anion **69**.



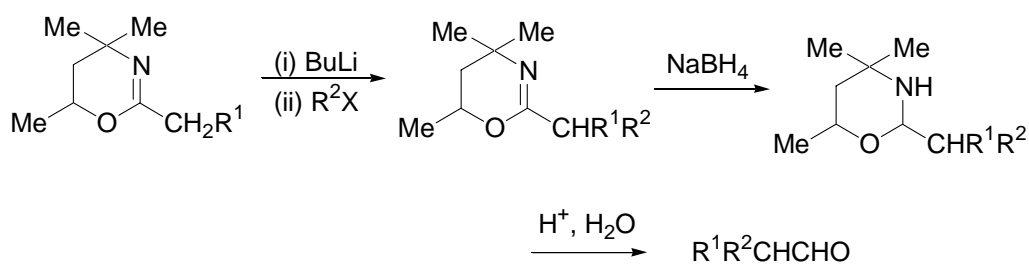


Figure 7.6.39. Formation of aldehydes by way of tetrahydrooxazines.

### 7.8.3 Phenothiazines

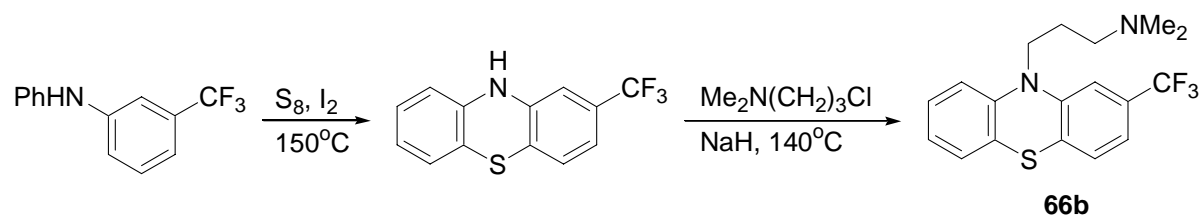


Figure 7.6.40. A route to triflupromazine.

