

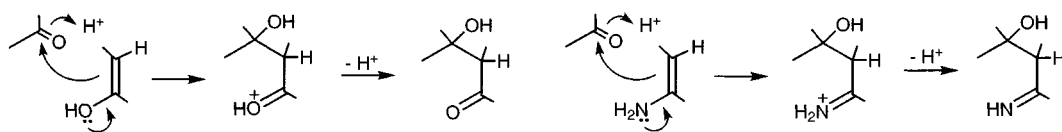
# 3 Synthesis of aromatic heterocycles

The preparation of benzenoid compounds nearly always begins with an appropriately substituted, and often readily available, benzene derivative – only on very rare occasions is it necessary to start from compounds lacking the ring, and to form it during the synthesis. The preparation of heteroaromatic compounds presents a very different picture, for it involves ring synthesis<sup>1</sup> more often than not. Of course when first considering a suitable route to a desired target, it is always important to give thought to the possibility of utilising a commercially available compound which contains the heterocyclic nucleus and which could be modified by manipulation, introduction and/or elimination of substituents<sup>2</sup> – a synthesis of tryptophan (section 17.12) for example would start from indole – however if there is no obvious route, a ring synthesis has to be designed which leads to a heterocyclic intermediate appropriately substituted for further elaboration into the desired target.

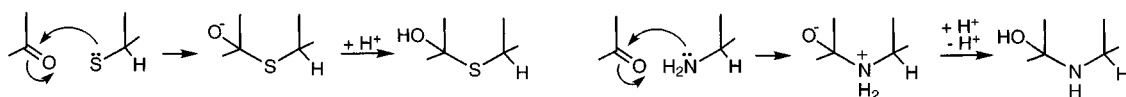
This chapter shows how just a few general principles allow one to understand the methods, at first sight apparently diverse, which are used in the construction of the heterocyclic ring of an aromatic heterocyclic compound from precursors which do not have that ring. It discusses the principles, and analyses the types of reaction frequently used in constructing an aromatic heterocycle, and also the way in which appropriate functional groups are placed, in the reactants, in order to achieve the desired ring synthesis.

## 3.1 Reaction types most frequently used in heterocyclic ring synthesis

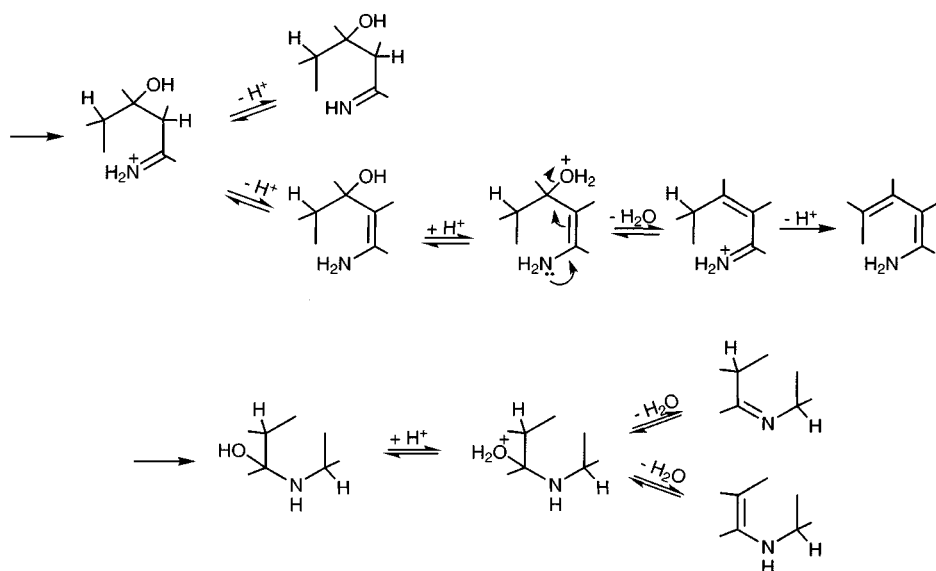
By far the most frequently used process is the addition of a nucleophile to a carbonyl carbon (or the more reactive carbon of an *O*-protonated carbonyl). When the reaction leads to C–C bond formation, then the nucleophile is the  $\beta$ -carbon of an enol or enolate anion, or of an enamine, and the reaction is aldol in type:



When the process leads to C–heteroatom bond formation, then the nucleophile is an appropriate heteroatom, either anionic ( $-X^-$ ) or neutral ( $-XH$ ):



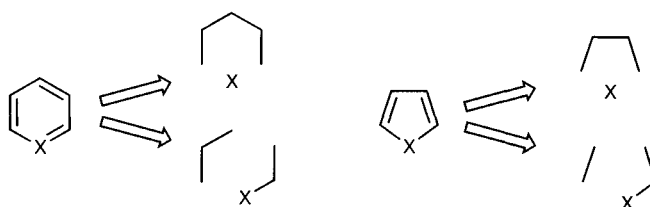
In all cases, subsequent loss of water produces a double bond, either a C–C or a C–heteroatom double bond. Simple examples are the formation of an aldol condensation product, and the formation of an imine or enamine, respectively.



These two basic processes, with minor variants, cover the majority of the steps involved in classical heteroaromatic ring synthesis. In a few instances, displacements of halide, or other leaving groups, from saturated carbon are also involved. In a completely separate categories are the increasing number of heterocyclic ring syntheses which involve electrocyclic processes (see section 3.4) and the use palladium(0)-catalysis in the ring forming step (section 2.7.2.4).

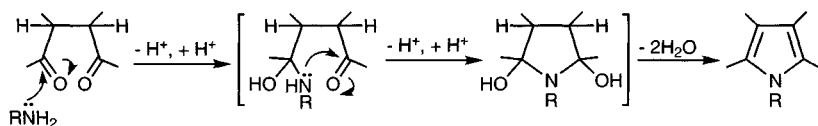
## 3.2 Typical reactant combinations

Although there are some examples of nearly all possible retrosynthetic dissections and synthetic recombinations of five- and six-membered heterocycles, yet by far the majority of ring syntheses fall into two categories; in the first, for each ring size, only C–heteroatom bonding is needed i.e. the rest of the skeleton is present intact in one starting component; in the second, for each ring size, one C–C bond and one C–hetero atom linkage are required.



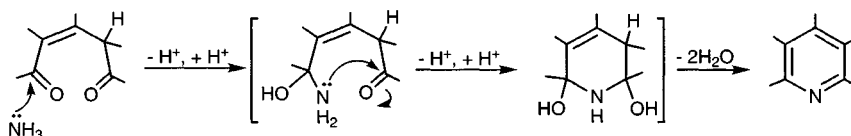
### 3.2.1

We can now look at more specific examples, and see how the principles above can lead to the aromatic heterocycles. In the first of the two broad categories, where only C–hetero atom bonds are needed, and for the synthesis of five-membered heterocycles, precursors with two carbonyl groups related 1,4 are required; 1,4-diketones, for example react with ammonia or primary amines to give 2,5-disubstituted pyrroles.



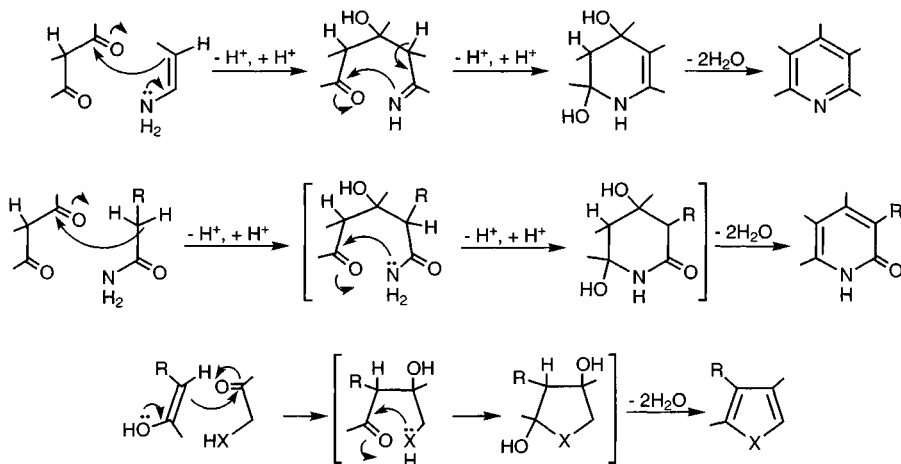
## 3.2.1.2

For six-membered rings, the corresponding 1,5-dicarbonyl precursor has to contain a C–C double bond in order to lead directly to the aromatic system (though it is relatively easy to dehydrogenate the dihydro-heterocycle which is comparably obtained if a saturated 1,5-dicarbonyl compound is employed).



## 3.2.2

In the second broad category, needing both C–C and C–hetero atom links to be made, one component must contain an enol/enolate/enamine, or the equivalent thereof, while the second obviously must have electrophilic centres to match. The following generalised combinations show how this works out for the two ring sizes.



Note: (1) The R substituent shown in the last two of these schemes must be an acidifying group: ketone, ester, nitrile, or occasionally, nitro.

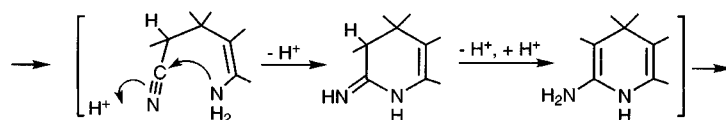
(2) Some of the components shown in these examples have two electrophilic centres and some have a nucleophilic and an electrophilic centre; in other situations components with two nucleophilic centres are required. In general, components in which the two reacting centres are either 1,2- or 1,3-related are utilised most often in heterocyclic synthesis, but 1,4- (e.g.  $\text{HX}-\text{C}-\text{C}-\text{YH}$ ) (X and Y are heteroatoms) and 1,5-related (e.g.  $\text{O}=\text{C}-(\text{C})_3-\text{C}=\text{O}$ ) bifunctional components, and also reactants which provide one-carbon units (formate, or a synthon for carbonic acid – phosgene,  $\text{Cl}_2\text{C}=\text{O}$ , or a safer equivalent) are also important. Amongst many examples of 1,2-difunctionalised compounds are 1,2-dicarbonyl compounds, enols (which first react in a nucleophilic sense at carbon and then provide an electrophilic centre (the

carbonyl carbon),  $\text{Hal}-\text{C}-\text{C}=\text{O}$ , and systems with  $\text{HX}-\text{YH}$  units. Amongst often used 1,3-difunctionalised compounds are the doubly electrophilic 1,3-dicarbonyl compounds and  $\alpha,\beta$ -unsaturated carbonyl compounds ( $\text{C}=\text{C}-\text{C}=\text{O}$ ), doubly nucleophilic  $\text{HX}-\text{C}-\text{YH}$  (amidines and ureas are examples), and  $\alpha$ -amino- or  $\alpha$ -hydroxycarbonyl compounds ( $\text{HX}-\text{C}-\text{C}=\text{O}$ ), which have an electrophilic and a nucleophilic centre.

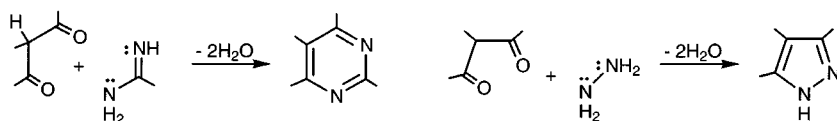
(3) The exact sequence of nucleophilic additions, deprotonations/protonations, and dehydrations is never known with certainty, but the sequences shown are the most reasonable ones; the exact order of steps almost certainly varies with conditions,<sup>3</sup> particularly  $\text{pH}$ .

(4) When components like  $\alpha$ -halocarbonyl compounds are utilised, and if reaction at the halogen-bearing carbon is a cyclising process, the displacement of the halogen (by enolate  $\alpha$ -carbon or heteroatom) is an *exo-tet* process. Where a cyclisation involves attack at carbonyl carbon or nitrile carbon and is the ring-closing step, the processes are *exo-trig* and *exo-dig* respectively.<sup>4</sup>

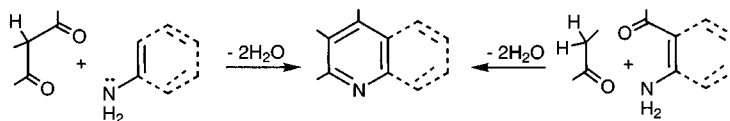
(5) In the second example above, where a carbonyl component (an amide) at the oxidation level of an acid is used then the resultant product carries an oxygen substituent at that carbon (pyridone in the example). Similarly, if a nitrile group is used instead of a carbonyl group, as an electrophilic centre, then the resulting heterocycle carries an amino group at that carbon, thus:



The two nucleophilic centres can both be heteroatoms, as in syntheses of pyrimidines and pyrazoles.

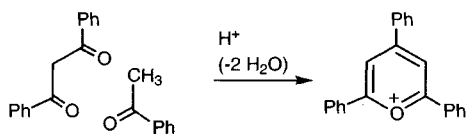


In syntheses of benzanellated systems, phenols can take the part of enols, and anilines react in the same way as enamines.<sup>5</sup>

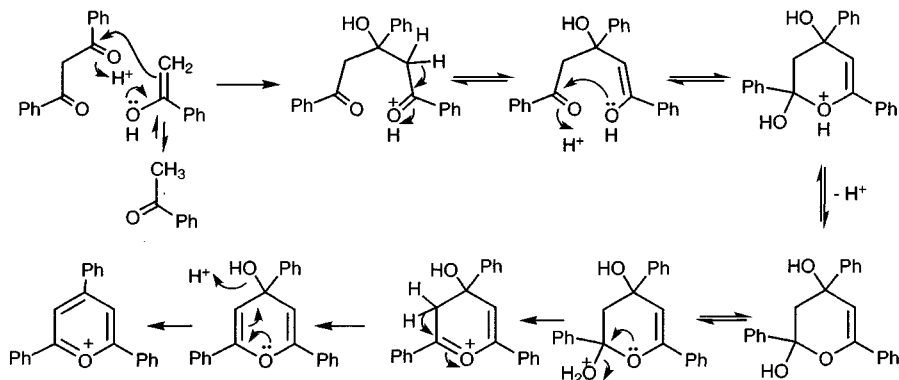


### 3.3 Summary

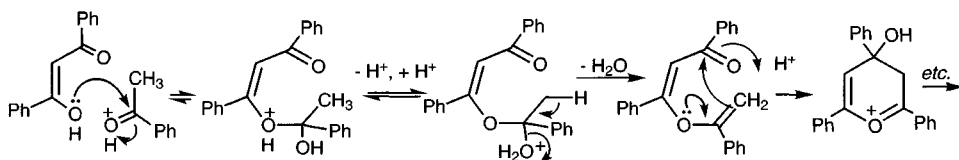
The chemical steps involved in heteroaromatic synthesis are mostly simple and straightforward, even though a first look at the structures of starting materials and product might make the overall effect seem almost alchemical. In devising a sequence of sensible steps it is important to avoid obvious pitfalls, like suggesting that electrophile react with electrophilic centre, or nucleophile with a source of electrons, but this aside it should be easy enough to devise a sensible scheme.



A complete step-by-step analysis of the reaction of 1,3-diphenylpropane-1,3-dione with acetophenone is presented below – note that many individual steps are involved but that each of them is very simple when considered separately.



The sequence shows an initiating step as nucleophilic attack by acetophenone enol on the protonated diketone, however an equally plausible sequence, shown below, starts with the nucleophilic addition of the enolic hydroxyl of the diketone to protonated acetophenone.



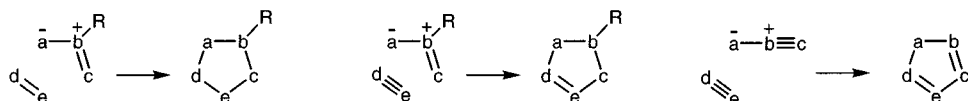
A final point to be made is that most of the steps in such sequences are reversible; the overall sequence proceeds to product nearly always because the product is the thermodynamically most stable molecule in the sequence, or because the product is removed from the equilibria by distillation or crystallisation. A nice example is the interrelationship between 1,4-diketones and furans; the latter can be synthesised by heating the former, in acid, under conditions which lead to the distillation of the furan (section 15.14.1.1), but in the reverse sense, furans are hydrolysed to 1,4-diketones by aqueous acid (section 15.1.1).

### 3.4 Electrocyclic processes in heterocyclic ring synthesis

There are two types of electrocyclic process which are of considerable value for heterocyclic ring synthesis: one of these is 1,3-dipolar cycloaddition, and the second involves a Diels-Alder type addition using some type of azadiene;<sup>6</sup> the latter does not in general produce aromatic heterocycles and, important though it is, will not be dealt with here.

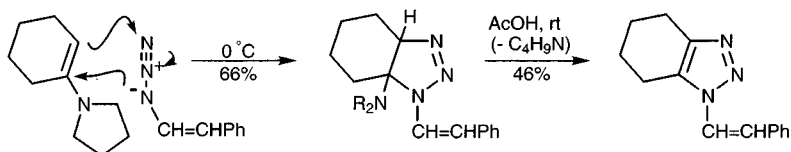
1,3-Dipoles always contain a heteroatom as the central atom of the trio, either  $sp$  or  $sp^2$  hybridised. Amongst other examples, cycloadditions have been demonstrated with azides ( $\text{N}\equiv\text{N}^+-\text{N}^--\text{R}$ ), nitrile oxides ( $\text{R}-\text{C}\equiv\text{N}^+-\text{O}^-$ ) and nitrile ylides ( $\text{R}-$

$C\equiv N^+-C^-(R_2)$  where the central atom is  $sp$  hybridised nitrogen, and with nitrones ( $R_2C=N^+(R)-O^-$ ), carbonyl ylides ( $R_2C=O^+-C^-(R_2)$ ), and azomethine ylides ( $R_2C=N^+(R)-C^-(R_2)$ ), where the central atom is  $sp^2$  hybridised.

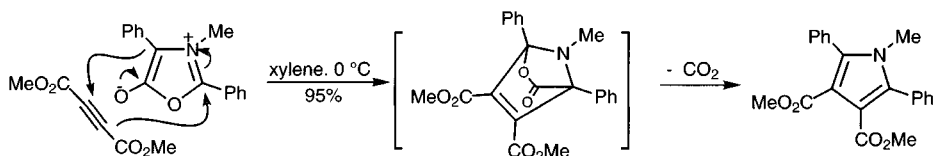


Dipolar cycloadditions<sup>7</sup> can, of course, only produce five-membered rings. Addition of dipolarophiles can generate tetrahydro, dihydro, or aromatic oxidation level heterocycles, as illustrated above. Alkene dipolarophiles with a potential leaving group, give the same result as equivalent alkyne dipolarophiles.

The interaction of azides, as the 1,3-dipoles, with enamines, followed by elimination of the amine, affords 1,2,3-triazoles.<sup>8</sup>

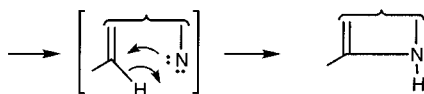


Many mesoionic substances (section 1.6) can act as 1,3-dipoles, and, after elimination of a small molecule – carbon dioxide in the example shown – produce aromatic heterocycles.<sup>9</sup>

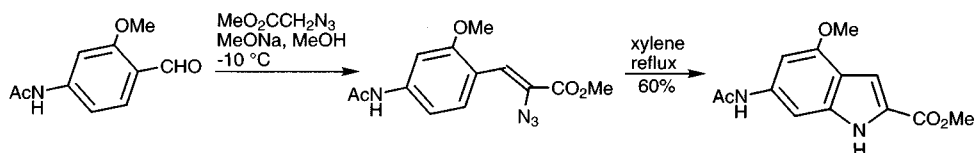


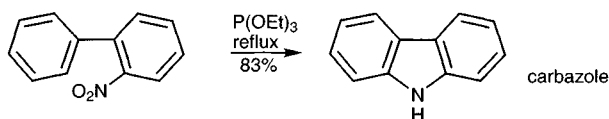
### 3.5 Nitrenes in heterocyclic ring synthesis<sup>10</sup>

The insertion of a nitrene (a monovalent, six-electron, neutral nitrogen, most often generated by thermolysis or photolysis of an azide ( $RN_3 \rightarrow RN + N_2$ ), or by deoxygenation of a nitro group) into a C–H bond has been made the key step in several synthetic routes to both five- and six-membered aromatic systems. The process can be written in a general way:



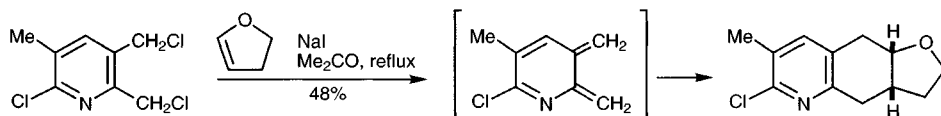
The preparation of an indole<sup>11</sup> (which was elaborated into the coenzyme, methoxatin (see also section 6.16.2.4), and of carbazole<sup>12</sup> illustrate the power of the method.



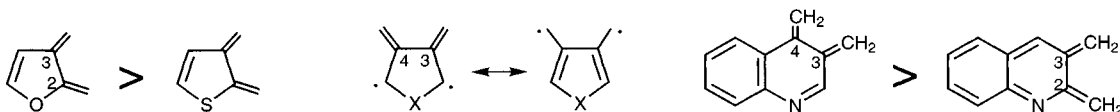


### 3.6 *ortho*-Quinodimethanes in heterocyclic compound synthesis<sup>13</sup>

The generation then trapping of *ortho*-quinodimethanes, in both intermolecular and intramolecular reactions, has become an important route for the construction of polycyclic heterocyclic compounds. This section describes the most important methods for the generation of such species, and gives some examples of their trapping. From the point of view of ring construction, the most important trapping reactions are those in which the *ortho*-quinodimethane acts as a diene in Diels-Alder cycloadditions, thereby regaining a fully aromatic ring, as illustrated below.<sup>14</sup> Apart from studies of spectroscopic and other physical properties, the unstable and reactive *ortho*-quinodimethanes are not isolated but are generated in the presence of the trapping reactant. Their adducts with sulfur dioxide can be a convenient way in which to store *ortho*-quinodimethanes generated by other means.

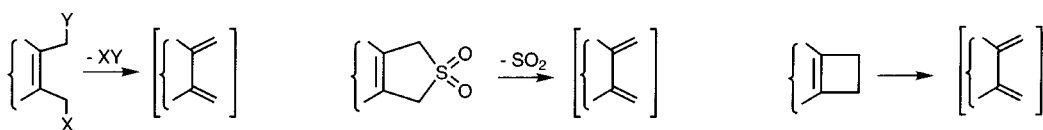


The ease with which an *ortho*-quinodimethane can be formed is related to the stability of the aromatic heterocycle from which it is derived and to the degree of double bond character between the *ortho* ring carbons. The first of these aspects can be nicely illustrated by comparing the thiophene 2,3-quinodimethane<sup>15</sup> with its furan counterpart<sup>16</sup> – the latter is more stable than the former – the thiophene-derived species has much more to lose in its formation from an aromatic thiophene (and much more to gain by reacting to regain that aromaticity) than does the latter.

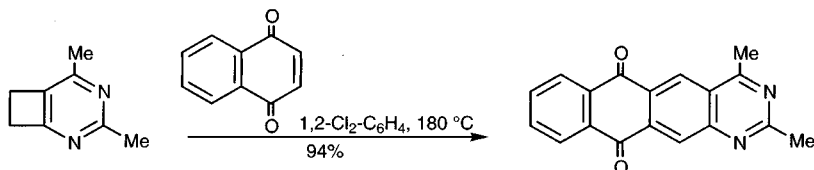


*ortho*-Quinodimethanes are much easier to produce if the bond between the *ortho* ring carbons in the precursor has considerable double bond character. Thus, in five-membered heterocycles, it is much easier to produce a 2,3-quinodimethane, than a 3,4-quinodimethane, indeed for the latter it becomes necessary to write resonating diradical structures implying a much higher energy. In bicyclic six-membered systems, for example quinolines,<sup>17</sup> it is much easier to produce 3,4-quinodimethanes than 2,3-quinodimethanes, structures for which imply a loss of resonance stabilisation in the second ring.

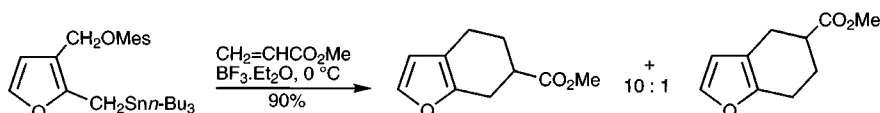
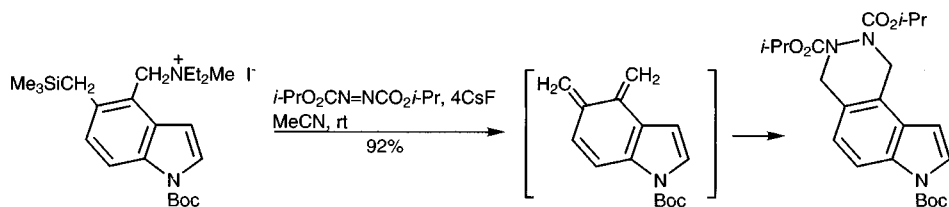
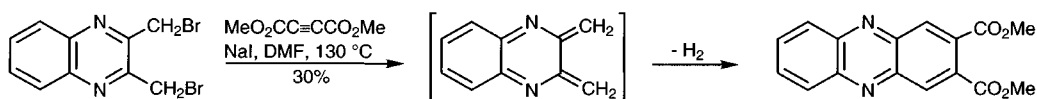
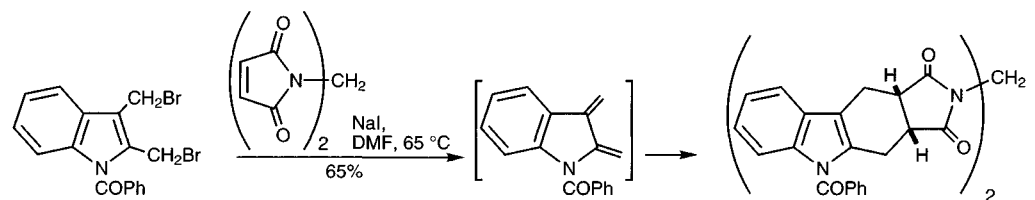
Three main strategies have been employed for the production of heterocyclic *ortho*-quinodimethanes: a 1,4-elimination, the chelotropic loss of sulfur dioxide from a 2,5-dihydrothiophene *S,S*-dioxide, and the electrocyclic ring opening of a cyclobutenoheterocycle; each of these is illustrated diagrammatically below.



The use of cyclobuteno-heterocycles is of course dependent on a convenient synthesis (for an example, see section 11.14.2.3), but when available, they are excellent precursors, only rather moderate heating being required for ring opening, as shown by the example below, in which the initial Diels-Alder adduct is aromatised by reaction with excess quinone.<sup>18</sup>

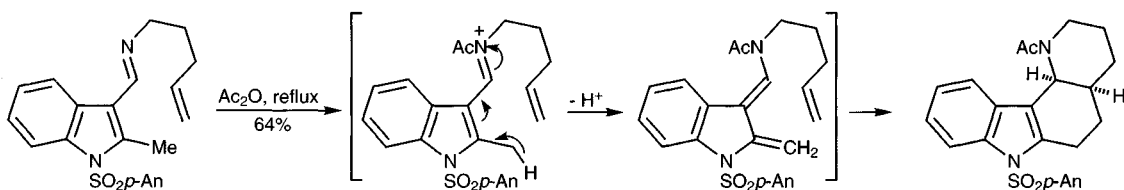


1,4-Eliminations have involved 1,2-bis(bromomethyl)-heterocycles with hot sodium iodide,<sup>19</sup> *ortho*-(trimethylsilylmethyl) heterenemethylammonium salts,<sup>20</sup> *ortho*-(trimethylsilylmethyl) heterenecarbinol mesylates,<sup>21</sup> each with a source of fluoride, and *ortho*-(tri-*n*-butylstannylmethyl) heterenecarbinol acetates with a Lewis acid.<sup>21</sup>

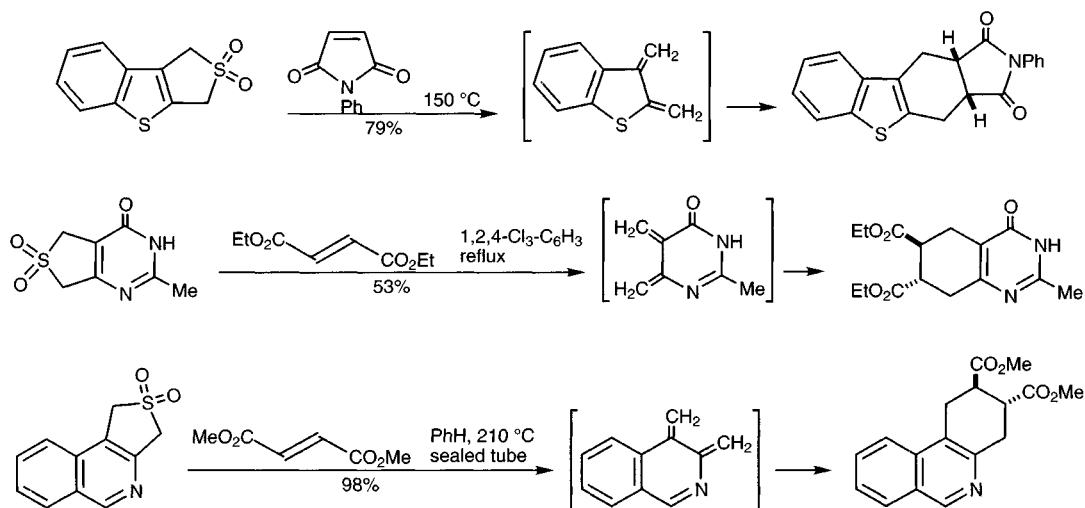


An extensively developed route involves loss of a proton from indol-3-ylcarboxaldehyde imines (or their pyrrolic counterparts<sup>22</sup>), following reaction with an acylating agent, as illustrated below.<sup>23</sup>





The extrusion of sulfur dioxide from heterocyclic sulfones is probably the most generally used method for the generation of *ortho*-quinodimethanes and many examples have now been reported. Such sulfones are generally stable and easy to synthesise, by various routes. In addition, the acidity of the protons adjacent to the sulfone unit allows for base-promoted introduction of substituents, before thermolytic extrusion and the Diels-Alder step. Three examples of sulfur dioxide extrusion are shown below.<sup>24</sup>



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