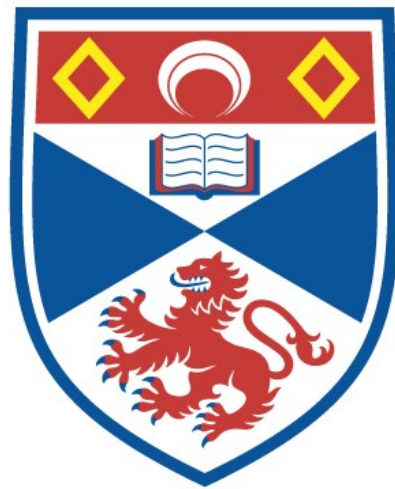# University of St Andrews

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1,2,4-Triazines and 1,2,4,5-Tetrazines as Monomers

for Diels-Alder Polymerisations

A thesis presented to the University of St. Andrews

for the degree of Master of Philosophy

by

Michael John Bruce

September 1994   University of St. Andrews

DEDICATION

To My Parents

CONTENTS

<u>Declaration</u>

I, Michael John Bruce, hereby certify that this thesis has been composed by me, that it is an accurate representation of the work undertaken by me in the University of St. Andrews since my admission as a Research Student on 1st October 1990, and that it has not been accepted in any previous application for any Higher Degree or professional qualification.

September 1994   Signed.

I hereby certify that Michael John Bruce has fulfilled the Regulations appropriate to the Degree.

September 1994   Signed.

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ACKNOWLEDGEMENTS

ABSTRACT

Chapter 1 (Introduction) comprises a brief overview of the origins, mechanism and scope of the Diels-Alder reaction. It deals with the three different Diels-Alder reaction types and highlights the utilisation of the reaction in general terms for the synthesis of aromatic and heteroaromatic ring systems. Particular attention has been paid to the inverse electron-demand Diels-Alder reactions of nitrogen-containing heterocycles, where aromatisation is brought about by the thermodynamically-driven loss of molecular nitrogen, leading to both carbocyclic and heterocyclic ring systems.

Chapter 2 (Results and Discussion) develops the ideas formed in Chapter 1 to seek possible bis-dienes and bis-dienophiles for utilisation in polymer synthesis. Attention has been concentrated on possible routes to bis-1,2,4-triazines and 1,2,4,5-tetrazines, which are novel compounds, and on their possible use in both inter- and intra-molecular Diels-Alder reactions.

A new method for the synthesis of bis-glyoxals involving the oxidation of the corresponding diacetyl-aromatics using HBr/DMSO is the most reliable and is capable of being scaled up without safety/environmental problems. The bis-glyoxals are then readily convertible into 5,5'-linked bis-1,2,4-triazines which are potential bis-dienes for Diels-Alder reactions. The attempted intermolecular reactions of the bis-triazines with a range of diethynyl-aromatics have, however, proved unsuccessful so far. Attempts to form bis-(*o*-ethynylphenols) for intramolecular Diels-Alder reactions after coupling to bis-triazines have also been unsuccessful.

Several 5-(substituted phenyl)-1,2,4-triazines have also been formed, with the intention of coupling these through the phenyl substituent to a central difunctional core. Several 1,2,4,5-tetrazines have been formed with similar intent.

Chapter 3 (Experimental) details the synthetic procedures and the **Bibliography** follows.

Chapter One

Introduction

Polymers containing an "all aromatic" backbone are of considerable current interest and importance for "high-performance" applications. The relative rigidity imposed on the polymer chain by the aromatic units helps to produce materials which possess high glass transition temperatures and/or melting points.

The high solvent resistance of some such materials can be ascribed to the chains packing together more easily than in many aliphatic polymers, and the high thermal stability of some of these materials results directly from the resistance of aromatic ring systems to oxidation in general. For example, many aromatic polyesters have very high levels of thermal stability and chemical resistance. These favourable characteristics, however, are lessened by the extreme difficulties encountered in the processing of such polymers, due to their very high melting points and/or low solubility in common solvents.

This problem has been overcome for some polymers such as PEEK (PolyEtherEtherKetone), commercially produced[1] by reaction of hydroquinone (Fig. 1.1) with 4,4'-difluorobenzophenone in the presence of sodium and potassium carbonates[2]. The reaction is facilitated by use of a high boiling dipolar aprotic solvent, diphenyl sulphone (DPS), and a final reaction temperature of not less than 300°C, in order to keep the polymer in solution until a sufficiently high molecular weight is attained[3].

The nature of any functional groups linking the aromatic units is of great importance in determining polymer properties. For example, for high-temperature applications the functional groups themselves should be resistant to oxidation. Functional groups which are planar or linear will assist in the spatial close packing of

the polymer chains, whereas groups which are tetrahedral, and thus more bulky, may lead to the polymer being more susceptible to solvent uptake and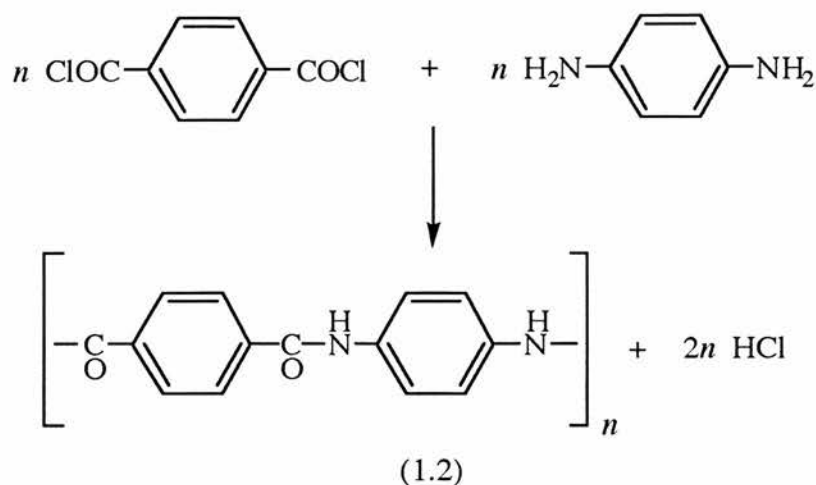 therefore potentially a weaker structural material. The susceptibility to solvent uptake may be a determining factor in, for example, the ease of hydrolysis of some polyesters.

It is not surprising that most aromatic polymers are made from functionalised monomers which already contain aromatic units, and the polymerisation step is a functional group transformation (for example, the formation of an ester/amide). Even a polymer such as PEEK is made by a nucleophilic aromatic substitution (Fig. 1.1).

(1.1)
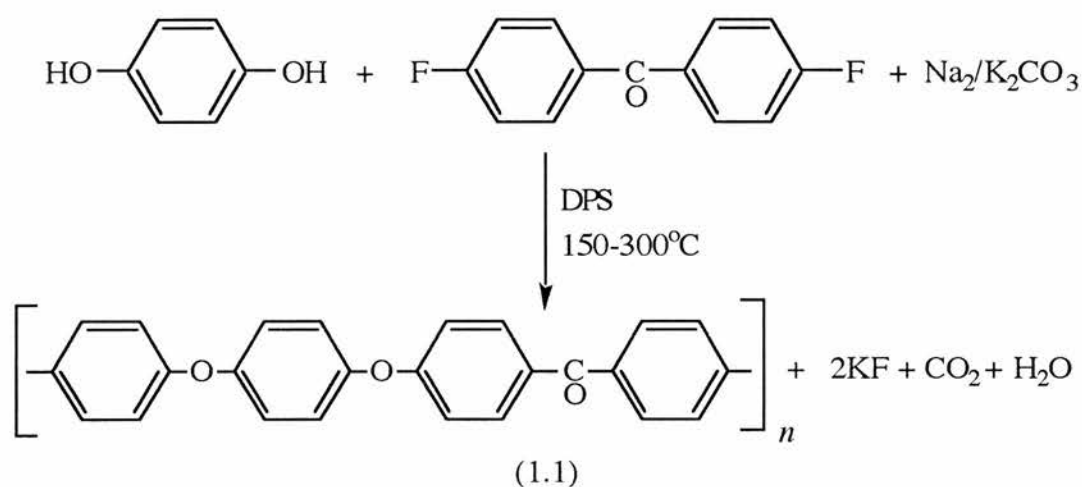
Another example of functional group transformation to effect a polymerisation process is in the general formation of aromatic polyamides (also known as aramids), which are used in the speciality fibre industry.

One such aramid, Kevlar (DuPont), is formed by the reaction of terephthaloyl chloride and p-phenylenediamine (Fig. 1.2). This compound has the tensile strength of steel[4] (at 20% weight), and an added advantage in that it is virtually nonflammable. It also has the added attraction of retention of its mechanical properties over a wide temperature range for prolonged time periods.

$$n \ ClOC{-}\langle\!\!\!\!\rangle{-}COCl \ + \ n \ H_2N{-}\langle\!\!\!\!\rangle{-}NH_2$$

$$\left[-\underset{O}{\overset{C}{\|}}{-}\langle\!\!\!\!\rangle{-}\underset{O}{\overset{C}{\|}}{-}\overset{H}{\underset{}{N}}{-}\langle\!\!\!\!\rangle{-}\overset{H}{\underset{}{N}}{-} \right]_n \ + \ 2n \ HCl$$

(1.2)

There are very few recorded examples of polymers where the polymerisation step actually involves the formation of an aromatic ring. This is scarcely surprising, given the number of aromatic compounds available and the relative scarcity of general methods for aromatic ring formation. However, the Diels-Alder reaction provides such an opportunity, for both benzenoid and heterocyclic ring formation, and the objective of this project is to explore the potential of the Diels-Alder reaction for the synthesis of aromatic and heteroaromatic polymers.

The Diels-Alder reaction is one of the most widely utilised reactions in synthetic organic chemistry. Although the thermal formation of 1:1 dimerisation products of selected dienes was first reported in 1906[5], it was the following observations and structural elucidation of 1:1 and 2:1 adducts derived from p-benzoquinone with selected dienes by Otto Diels and Kurt Alder[6] which brought the reaction to prominence. From then it has grown to be one of the fundamental methods for carbocyclic and heterocyclic ring formation[7].

The reaction is a $[\pi^4 s + \pi^2 s]$ thermal cycloaddition in which a conjugated diene moiety $[\pi^4 s]$ undergoes a stereospecific addition reaction with another component, called a dienophile $[\pi^2 s]$, most commonly an activated olefin or acetylene. Initial studies on the reaction simply defined the regioselectivity and stereoselectivity accompanying the thermal $[\pi^4 s + \pi^2 s]$ cycloaddition and this gave the basis for

understanding of the reaction mechanism, which was seen to be a concerted bimolecular process.

Extensive studies[8-11] on this mechanism have shown that, while not all Diels-Alder cycloadditions can be described in terms of one mechanism, the vast majority of thermal cycloadditions can be assigned this symmetry-allowed one-step mechanism. Once these important factors were understood, it was then possible to predict products from the reaction process[12].
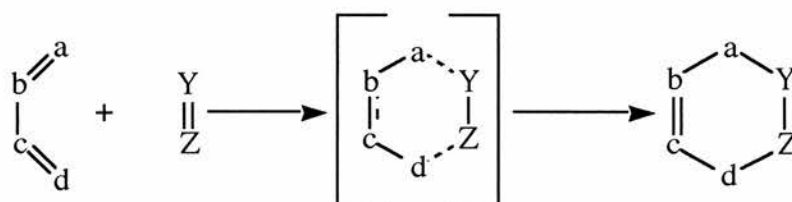
(1.3)

Studies on the reactivity and selectivity have been used in tandem with Frontier Molecular Orbital (FMO) theory[8,13-18] to give the basis for subclassification of the Diels-Alder reaction, and there have been three general reaction types classified[19] which are dependent on the three possible arrangements of the Highest Occupied Molecular Orbital [HOMO] and the Lowest Unoccupied Molecular Orbital [LUMO] (Fig. 1.4). These types are as follows:-

(1) Normal Diels-Alder reactions

(2) Neutral Diels-Alder reactions

(3) Inverse electron-demand Diels-Alder reactions.

$$D = Diene$$
$$Dp = Dienophile$$

Normal   Inverse   Neutral

(1.4)
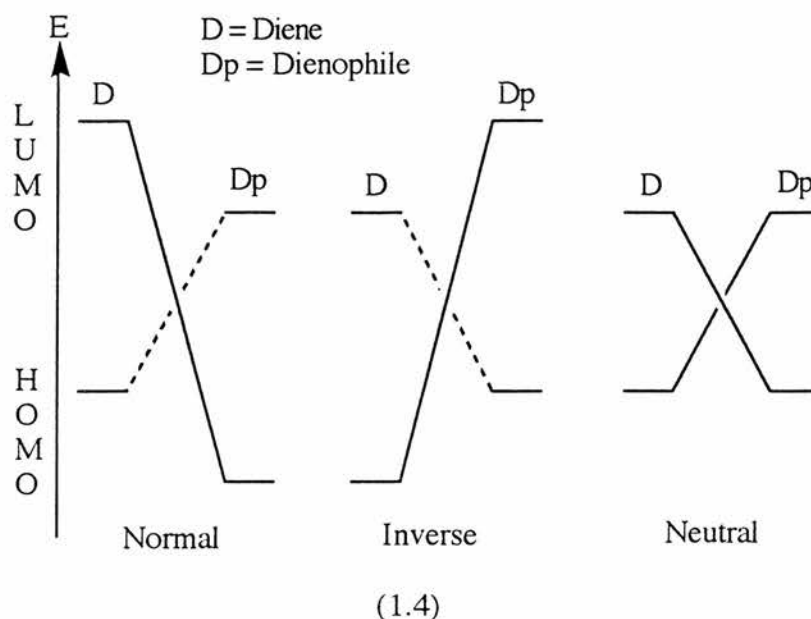
In these reaction types, the reaction rate is dependent on the magnitude of the lowest HOMO-LUMO energy separation that can be attained by the reacting diene/dienophile[20].

All factors that lessen the HOMO-LUMO distance increase the reaction rate due to the smaller difference in energy between interacting FMO's, since the stabilisation of the transition state is increased. There are two possible types of FMO interaction for the Diels-Alder reaction:-

[1] $HOMO_{diene}$-$LUMO_{dienophile}$

[2] $LUMO_{diene}$-$HOMO_{dienophile}$
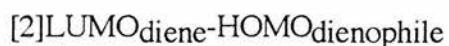
For normal Diels-Alder reactions the dominating molecular orbital interaction is that of the $HOMO_{diene}$-$LUMO_{dienophile}$ (this is in accordance with the lowest HOMO-LUMO energy separation). For inverse electron-demand Diels-Alder reactions however, the controlling molecular orbital interaction is between the $LUMO_{diene}$-$HOMO_{dienophile}$ and for neutral Diels-Alder reactions, neither frontier orbital separation dominates.

W = electron-withdrawing group
D = electron-donating group

(1.5)
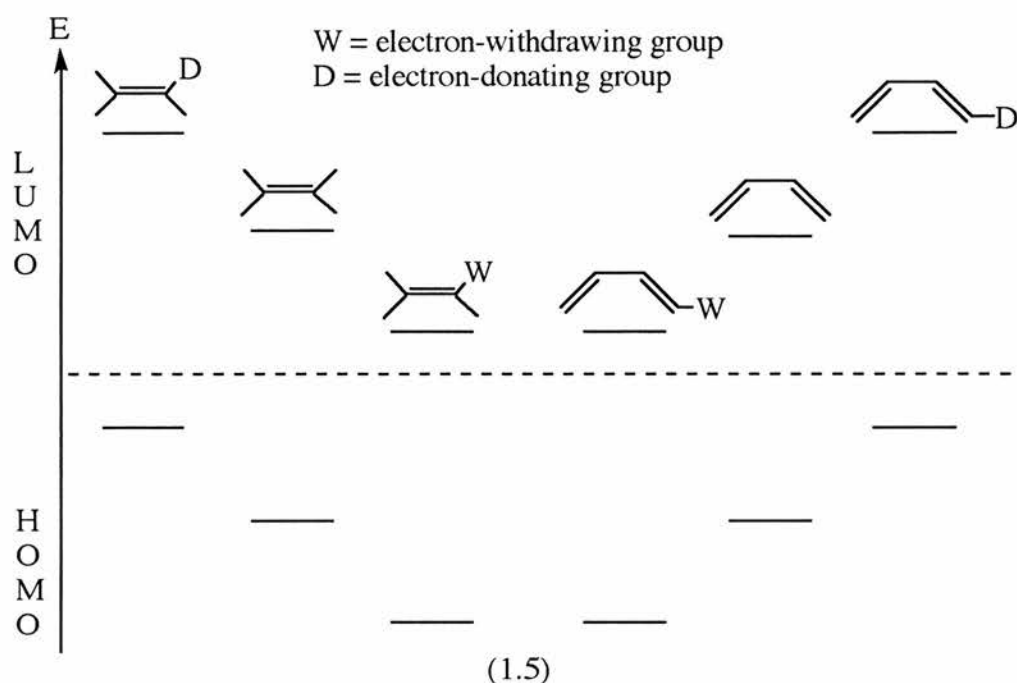
This reactivity can be explained on the basis of the energy changes that substituents cause on the molecular orbitals of both the diene and the dienophile. It is seen that the energies of both the HOMO and LUMO molecular orbitals are lowered when electron-withdrawing substituents are present, as opposed to an increase in their energies when there are electron-donating substituents attached (Fig. 1.5).

As can be seen (Fig. 1.6), for the normal Diels-Alder reaction, electron-donating substituents on the diene increase the reaction rate, whereas electron-withdrawing substituents retard the reaction progress. Electron-withdrawing sustituents on the dienophile increase the reaction rate but electron-donating groups retard the reaction rate.

For the inverse electron-demand reaction (Fig. 1.7) it is seen that the electronic effects are the opposite of those of the normal Diels-Alder reaction, with electron-withdrawing groups on the diene enhancing the reaction rate, while electron-donating groups hinder the reaction. For the dienophile, however, electron-withdrawing groups will retard the reaction, whilst electron-donating groups will enhance the reaction rate[21].

Normal electron demand Diels-Alder reaction

E

LUMO

HOMO

Dienophile

Diene

D

ΔE

ΔE

$\Delta E'$

H
O
M
O

W

W = electron-withdrawing group
D = electron-donating group

(1.6)

Inverse electron demand Diels-Alder reaction

E

Diene

D

LUMO

W

HOMO

$\Delta E'$

ΔE

ΔE

Dienophile

W = electron-withdrawing group
D = Electron-donating group
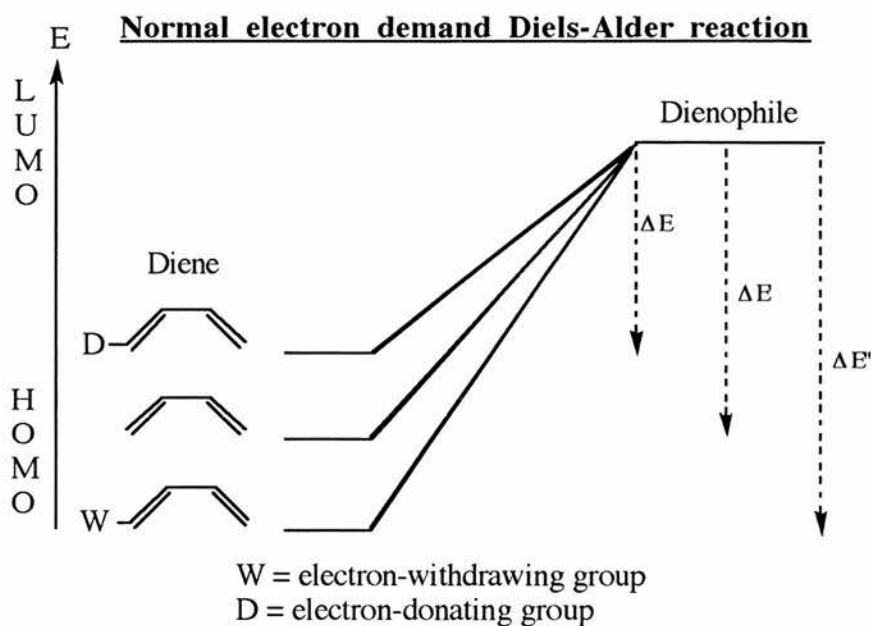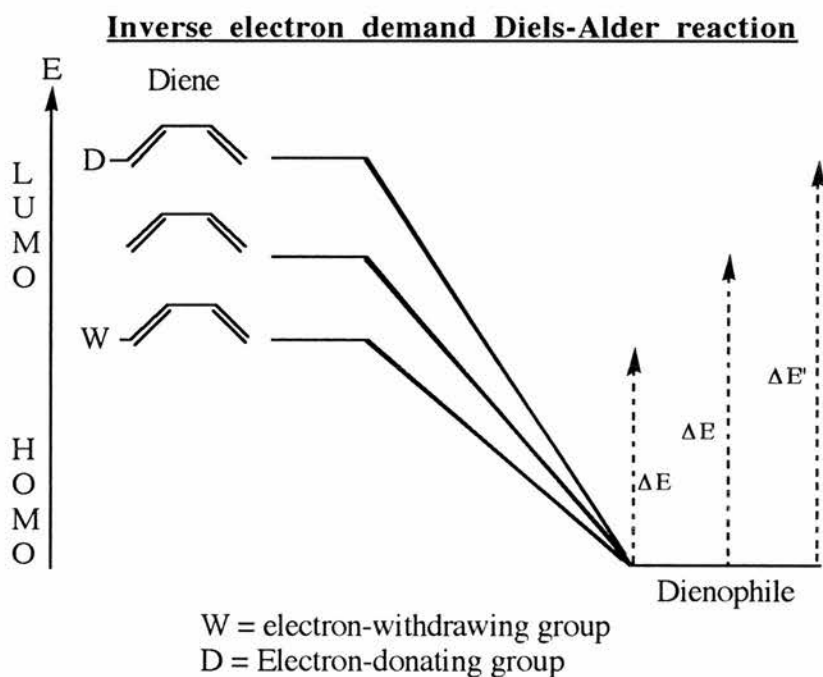
(1.7)

Thus it can be stated that the normal [$HOMO_{diene}$-controlled] Diels-Alder reaction employs an electron-rich diene (increased energy of the $HOMO_{diene}$) and an electron-deficient dienophile (decreased $LUMO_{dienophile}$ energy), whereas the inverse electron-demand [$LUMO_{diene}$-controlled] Diels-Alder reaction utilises an electron-

deficient diene (decreased $LUMO_{diene}$ energy) and an electron-rich dienophile (increased $HOMO_{dienophile}$ energy). In the neutral Diels-Alder reaction both frontier orbital interactions are involved[22] (HOMO-LUMO-controlled).

The Diels-Alder reaction is a reversible cycloaddition reaction, and as such involves an equilibrium between starting materials (diene/dienophile) and products (adducts). The retro-Diels-Alder reaction may be brought about simply by heating the adduct and/or removing one of the original components (e.g. by distillation).

For an essentially irreversible reaction to occur, there has to be a driving force to favour product formation, and one possible method for this is by expulsion of a small molecule from the initial cycloadduct. If this expulsion leads to the formation of a stable system, for example an aromatic ring, then the driving force is considerably increased. In this connection, much research has been done on tetraphenylcyclopenta-dienone ('tetracyclone') (Fig. 1.8) and other cyclopentadienones[23].
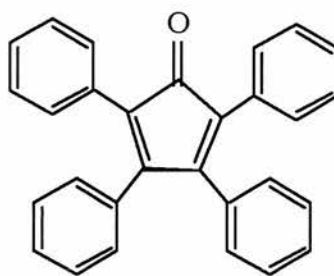
(1.8)

Certain cyclopentadienones can undergo a Diels-Alder dimerisation reaction (Fig. 1.9) in which one molecule acts as diene and the other as dienophile[23]. The equilibrium position depends on attached substituents and two products are possible, a non-dissociating dimer or a dissociating dimer, the rule being that the more bulky the substituents, the more likely the dissociating dimer is formed as steric contraints lower the dissociation energy. Certain non-dissociating dimers have been heated and the reaction is not one of dissociation but of expulsion of carbon monoxide to give a fused ring product. As previously stated, the limiting factor for this dimeric association is the

bulkiness of the substituents on the cyclopentadiene ring, with the extreme case existing of monomeric cyclopentadienones having very bulky substituents[24].

(1.9)
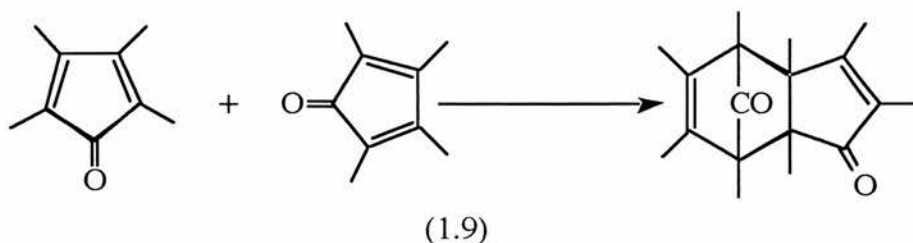
Use of heat in the reaction of certain monomeric cyclopentadienones with alkenes can lead to the formation of stable aromatic compounds (Fig. 1.10). In such reactions, dihydrobenzenes have been isolated, and it is thus reasonable to state that the reaction involves the initial formation of a bridged carbonyl compound; then the expulsion of carbon monoxide[25,26] (Fig. 1.10-[1]) leads to the dihydro compound with subsequent elimination (Fig 1.10-[2]) yielding the fully aromatised product. The formation of the aromatic system can also, for some reactions, be a 'one-pot' reaction, where no intermediate is isolated (Fig. 1.10-[3]).

(1.10)
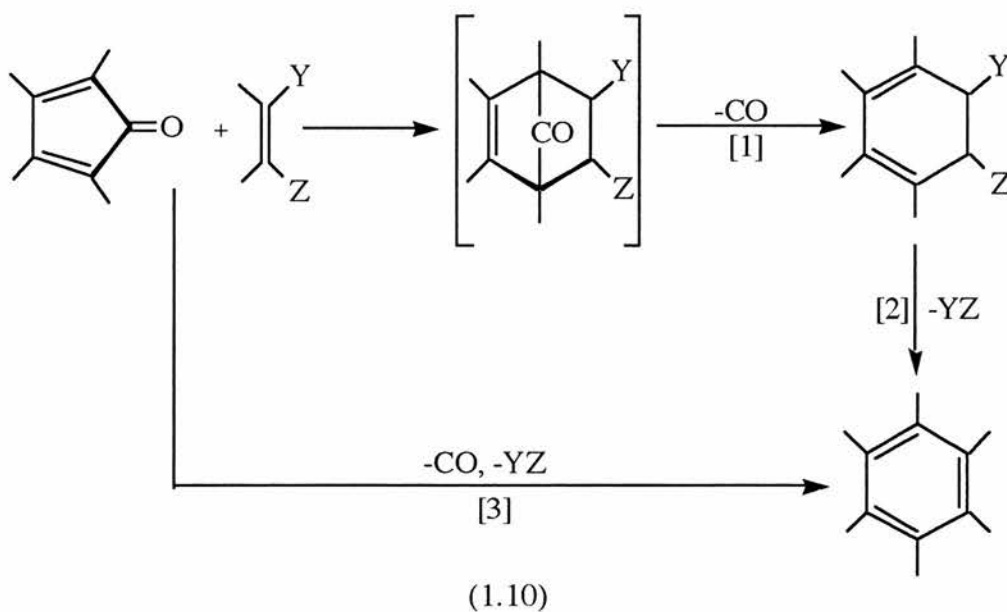
With alkynes, a similar reaction pattern is observed (Fig. 1.11). Again, the formation of a bridged carbonyl intermediate is possible, with carbon monoxide expulsion giving the aromatic ring directly. The main advantage of using alkynes is that there is direct formation of the aromatic compounds, without the need for dihydro

intermediates, and reaction conditions are generally milder than for the corresponding reactions with alkenes[27].

(1.11)
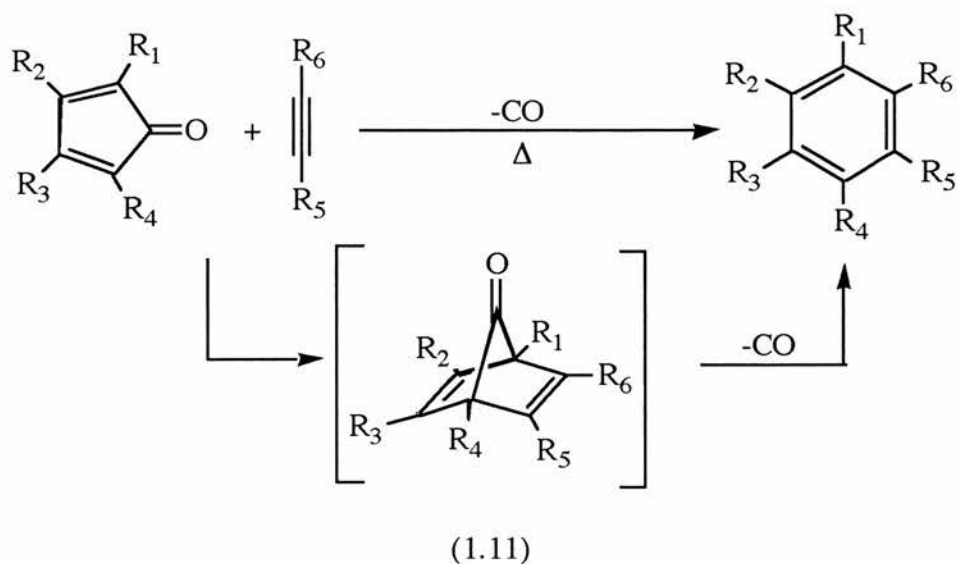
A specific example of this is the reaction of benzyne with substituted tetracyclones (Fig. 1.12), and studies[28] have shown that electron-donating substituents on the diene enhance the reaction yield.

$R = H, OCH_3, N(CH_3)_2$

(1.12)
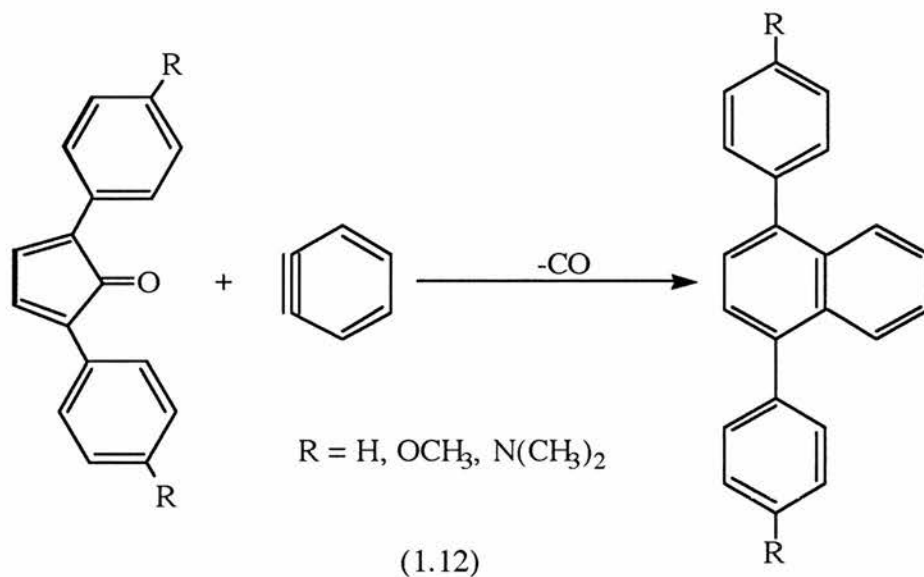
Heterocyclic ring formation is also possible using tetracyclone, as the reaction with nitriles has shown[29], with substituted pyridines being produced (Fig. 1.13), but reaction conditions are markedly more severe than for acetylenic reactions, with temperatures in excess of 300°C needed for prolonged periods.

(1.13)
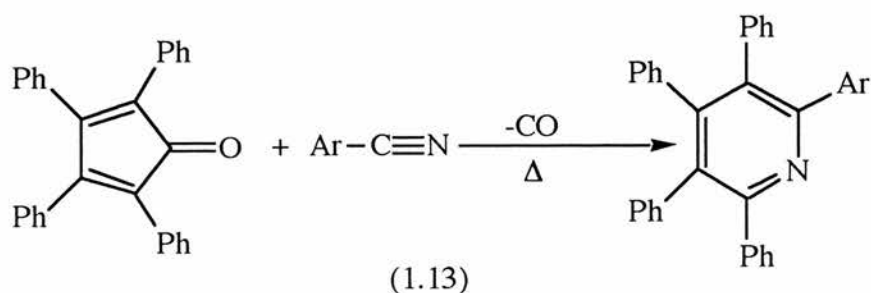
It was also seen that additional electron-withdrawing substituents on the nitrile accelerated the reaction. Reaction rates of tetracyclone with subtituted nitriles/alkynes have been examined[29,30] (determined by cessation of carbon monoxide production) and it was found that electron-withdrawing substituents on the dienophile accelerate the reaction. Thus, reactions undergone by substituted tetracyclones to form carbocyclic and heterocyclic systems appear to be normal electron demand Diels-Alder reactions.

These Diels-Alder reactions are not only used with carbocyclic starting materials, as shown by related reactions using α-pyrones. Both dienic and dienophilic nature may be displayed by α-pyrones, with the latter case predominating if an additional electron-withdrawing substituent[31] (Fig. 1.14) is present, resulting in the role of the α-pyrone in the reaction being primarily that of an electron-deficient dienophile (normal Diels-Alder reaction).

(1.14)
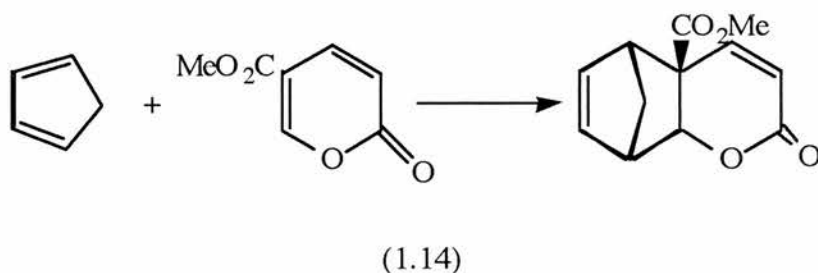
The most important Diels-Alder reaction of α-pyrones is their utilisation as dienes with various dienophiles. For olefinic reactions (Fig. 1.15), bridged adducts are initially formed (Fig. 1.15[1]), with subsequent carbon dioxide expulsion upon heating (Fig. 1.15[2]) yielding dihydrobenzenoid systems[32].

(1.15)
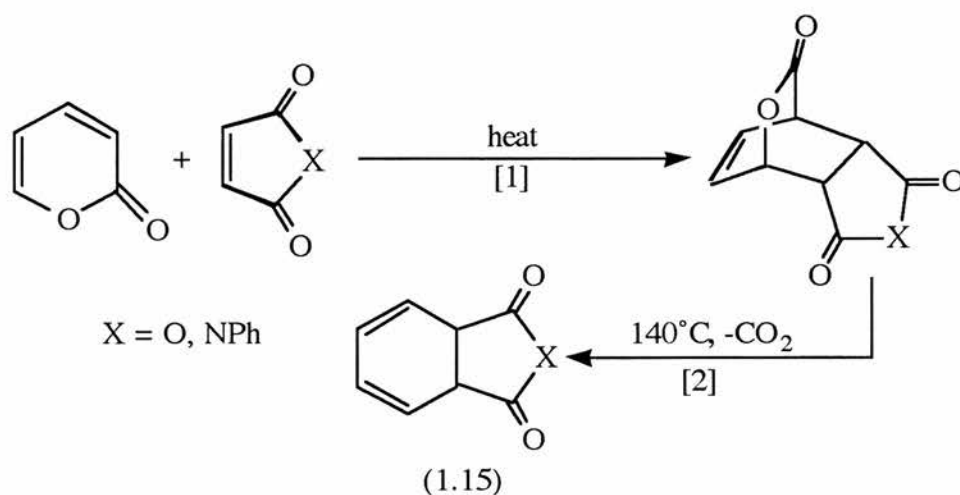
This reaction method can also be extended to reactions with alkynes (as in tetracyclone reactions), with one step aromatic ring formation/carbon dioxide expulsion (Fig. 1.16) being possible under less severe conditions[33,34]. Indeed, amongst the known bicyclic adducts with endo bridges, the monoadducts of α-pyrones are the least stable upon heating, with decomposition of certain adducts at temperatures as low as 60°C and only in rare instances can they withstand heating above 130-140°C.

(1.16)
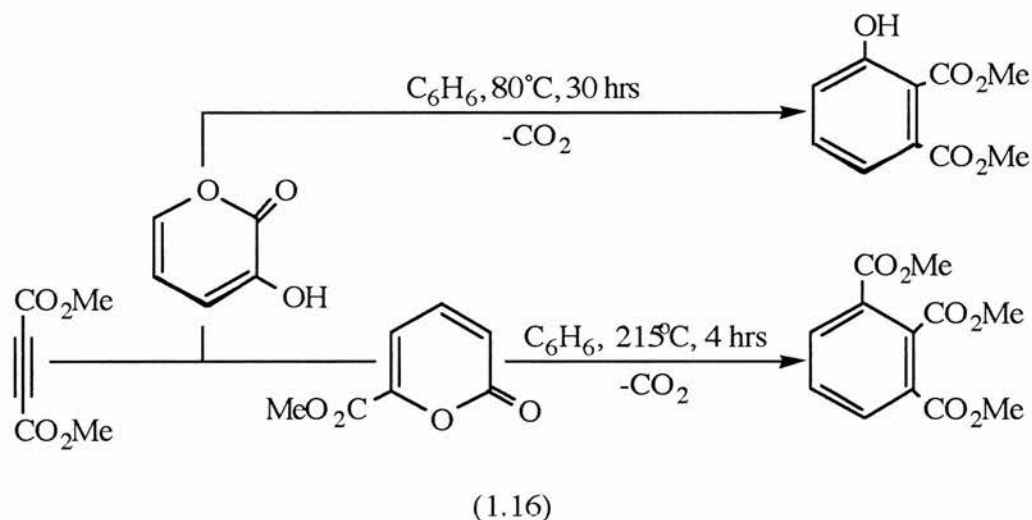
Again, electron-withdrawing groups on the dienophile and electron-donating groups on the diene enhance the reaction progress, giving rise to normal electron demand Diels-Alder reactions. The main difference between the reactions of substituted tetracyclones and α-pyrones is the nature of the molecule expelled. In the former case it is carbon monoxide, whereas in the latter case it is carbon dioxide.

Another important example of utilisation of Diels-Alder reactions for conversion from heterocyclic systems to stable aromatic compounds are reactions of pyridazines with various dienophiles. Dienophiles which have been extensively studied are substituted alkenes[35] and ynamines[36]. For reaction with substituted alkenes, for example using 1-methoxy-1-(dimethylamino)ethylene as the dienophile, it is seen that the bridged cycloadduct is initially formed (Fig. 1.17), with cycloaddition occurring across the C-3/C-6 position of the 1,2-diazine nucleus. Expulsion of molecular nitrogen from the bicycloadduct followed by elimination of methanol/dimethylamine results in formation of the aromatic system.

(1.17)
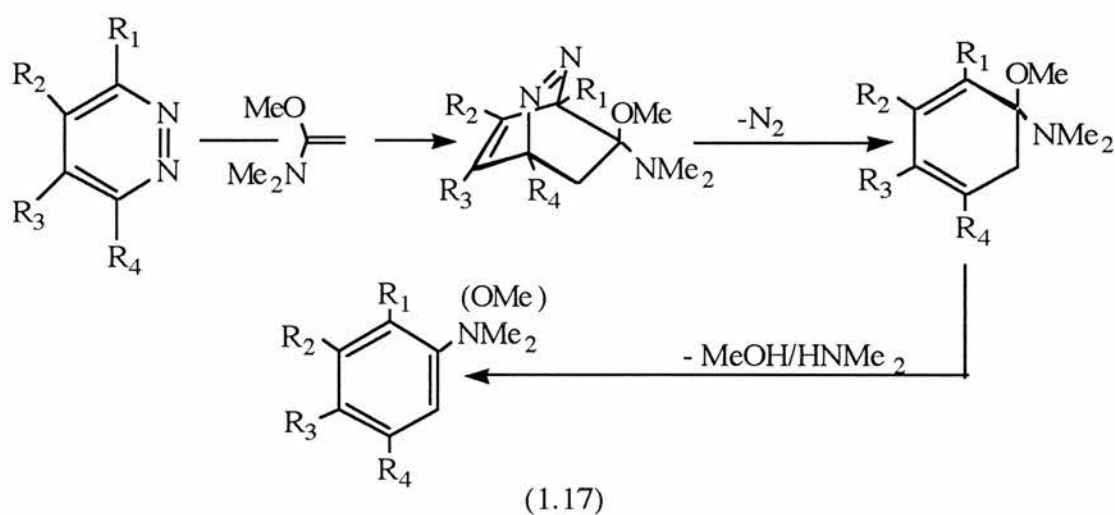
An exception to this general scheme is in the reaction of ynamines with electron-deficient pyridazines, with two modes of cycloaddition possible (Fig. 1.18), the first being addition across C-3/C-6[A] which leads to formation of substituted aromatic systems by elimination of molecular nitrogen. Alternatively, the route of addition can be across N-1/C-4[B] of the diazine nucleus, which upon expulsion of a nitrile leads to substituted pyridine systems.

These cycloaddition modes and the regiospecificity are seen to be strongly dependent on the number and position of electron-withdrawing substituents present on the diazine nucleus, with each distinct substituent pattern only having one reaction product[36b]. It is noted that the reactions occurring are inverse electron-demand Diels-Alder reactions, with electron-deficient dienes and electron-rich dienophiles involved.

(1.18)
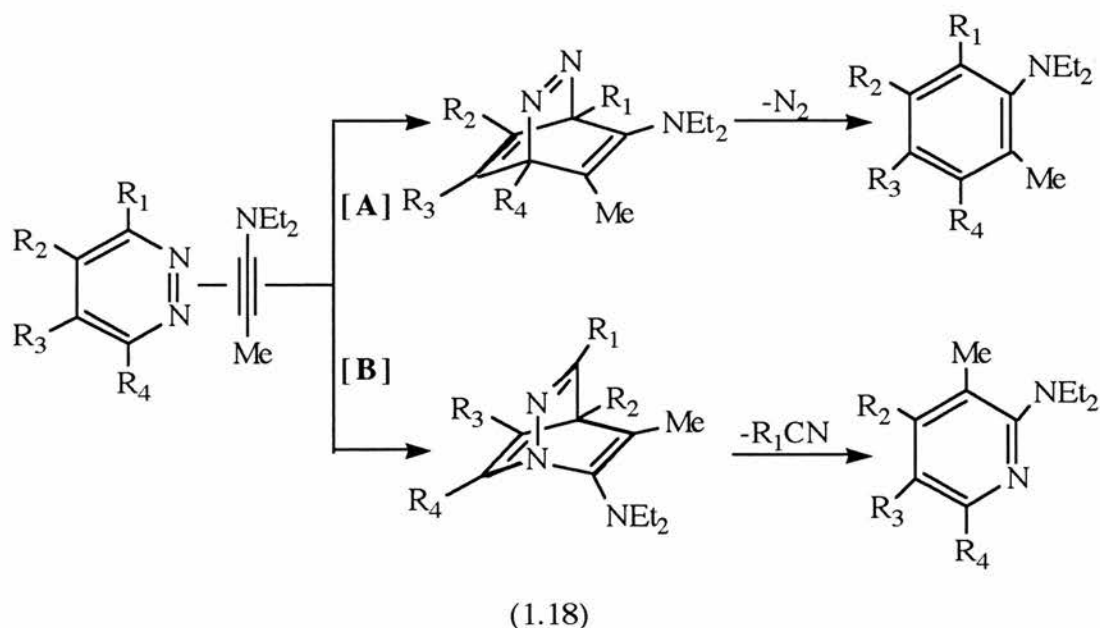
Use of the other two diazine systems, namely the pyrimidines (1,3-diazines) and the pyrazines (1,4-diazines) as dienes in Diels-Alder reactions has been studied, with the formation of various substituted pyridines for both systems. For the 1,3-diazine systems, addition of electron-withdrawing substituents to the pyrimidine nucleus accelerates the rate and ease of reaction with electron-rich dienophiles (Figs. 1.19 and 1.20) in inverse electron-demand cycloaddition reactions.

(1.19)
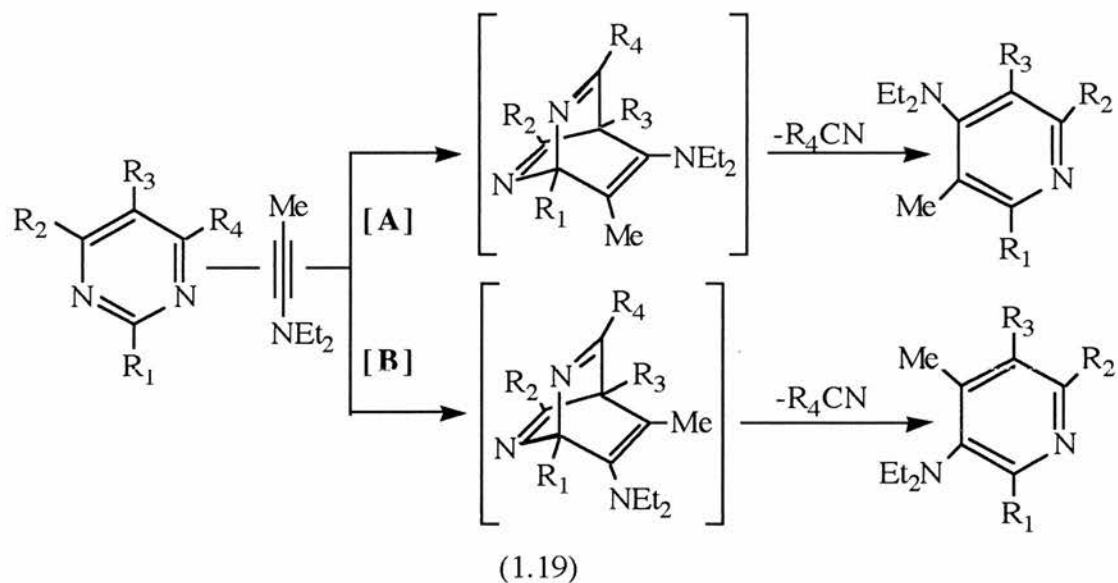
Again the regioselectivity and mode of cycloaddition observed (across C-2/C-5 (Fig 1.19)[37] or N-1/C-4 (Fig. 1.20)[38]) are dependent on the number and position of

diene substituents and the nature of the dienophile (i.e. alkyne/alkene). In Figure 1.19, it is observed that there is a strong preference for the nucleophilic carbon of the ynamine to be attached to C-2 of the pyrimidine nucleus [**B**] unless there are adequate electron-withdrawing substituents attached for sufficient reduction of the electron density at C-5 [**A**].

(1.20)
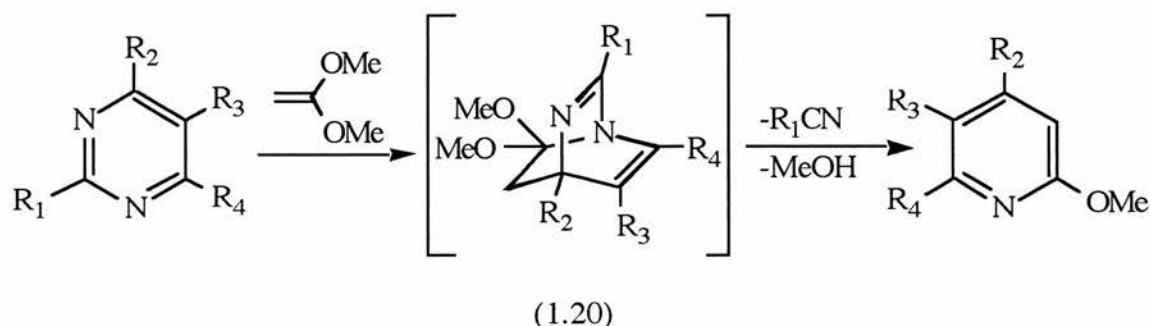
However, insertion of two (or three) electron-donating groups into the pyrimidine nucleus at C-2, C-4 (and C-6) allows the pyrimidines to undergo normal electron demand Diels-Alder reactions with electron-deficient alkynes[41] (Fig.1.21).

(1.21)
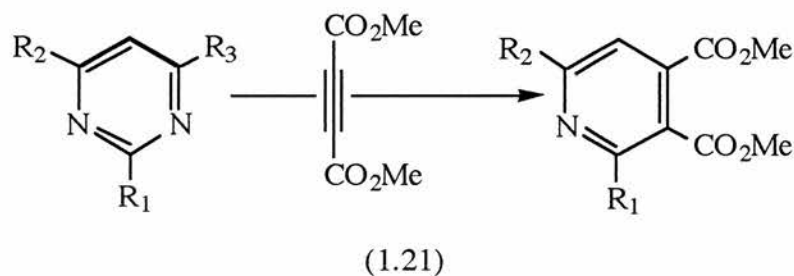
For pyrazines, an inverse electron-demand Diels-Alder reaction can occur by reaction of electron-deficient 1,4-diazines with 1-(diethylamino)propyne (Fig. 1.22), giving rise to substituted pyridines[40]. Figure 1.22 shows four of the eight possible pyridines formed, the other four having the methyl and diethylamino positions reversed. As before, both the reaction rate and the regioselectivity observed are dictated by the number and position of electron-withdrawing groups on the pyrazine nucleus. There is only one observed mode of cycloaddition (across C-2/C-5) for these compounds, but it is seen that there are several possibilities for the substituent on the nitrile expelled from the molecule. Alternatively, electron-rich pyrazines can react with electron-deficient and strained dienophiles in a normal electron-demand Diels-Alder

reaction[41]. An example is the reaction of substituted 2,5-dihydroxypyrazines with dimethylacetylenedicarboxylate to yield pyridone derivatives (Fig 1.23).

(1.22)

(1.23)
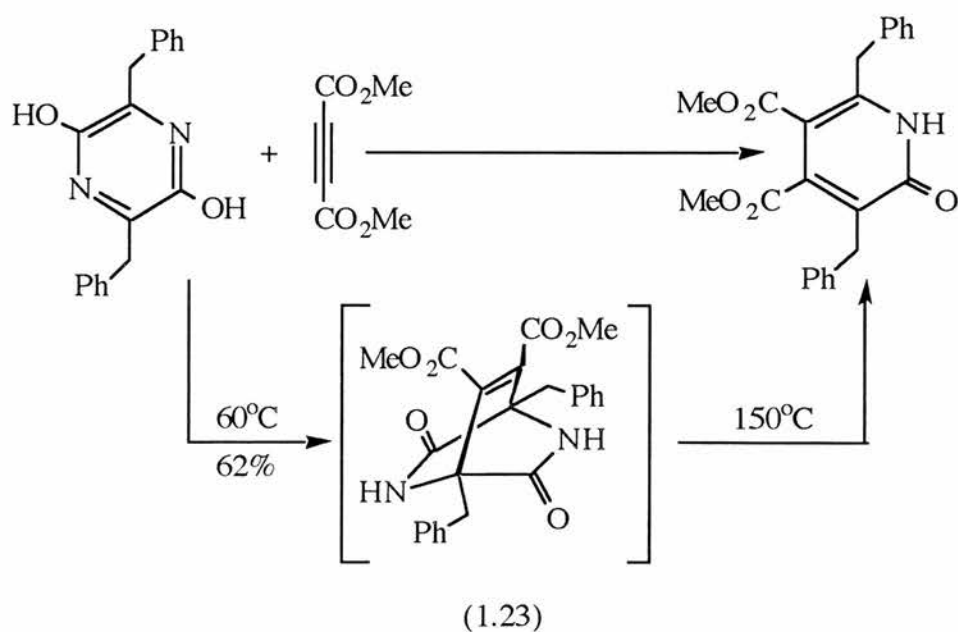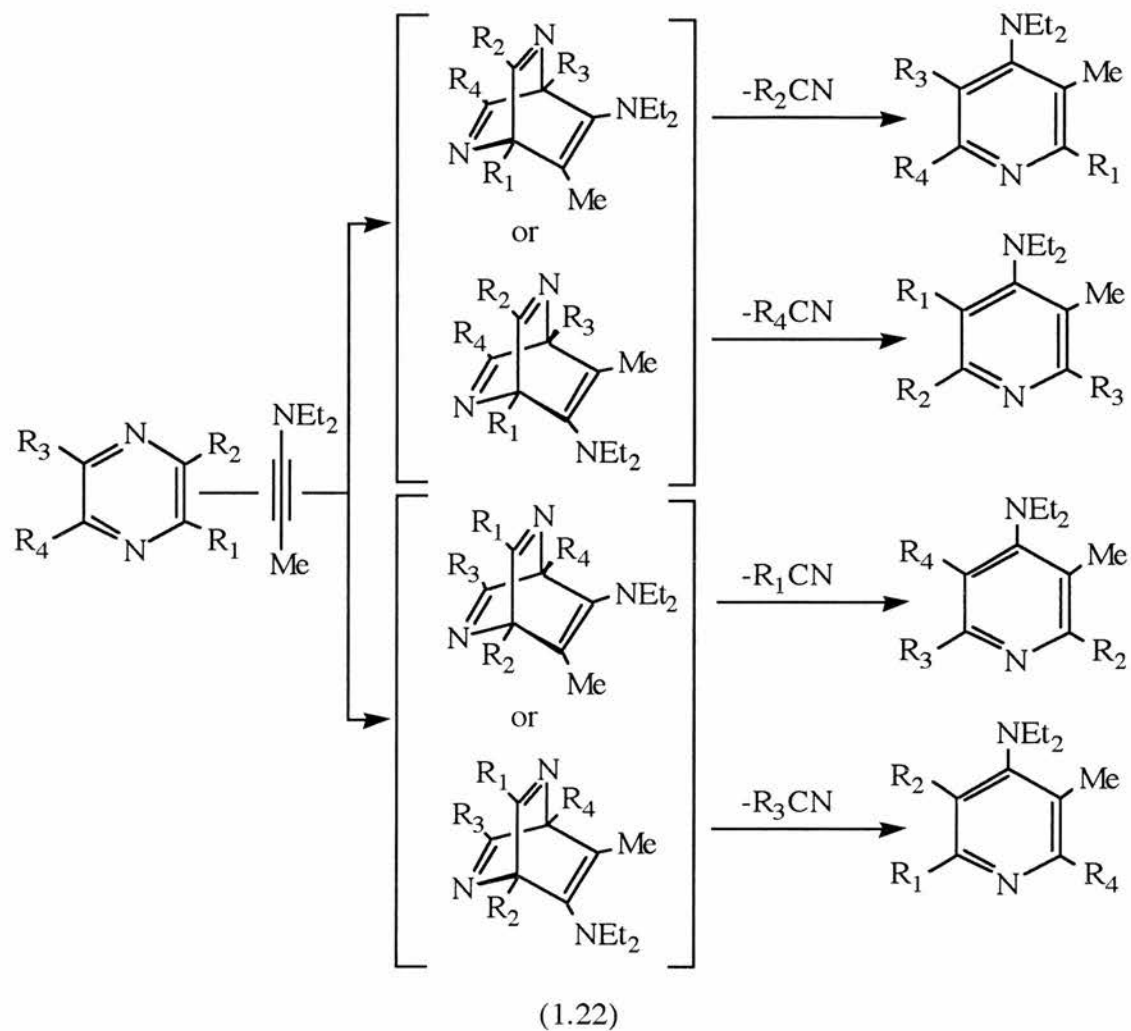
The concept of using heterocycles containing three or more nitrogens as dienes in Diels-Alder reactions has been extensively researched. Substituted 1,3,5-triazine (s-triazine) nuclei are sufficiently electron-deficient that they can readily participate in inverse electron-demand cycloaddition reactions[42,43] with electron-rich dienophiles (Fig. 1.24). It has been observed that addition of electron-withdrawing substituents on the triazine nucleus will accelerate the rate of triazine participation in inverse electron-demand Diels-Alder reactions[42].

(1.24)
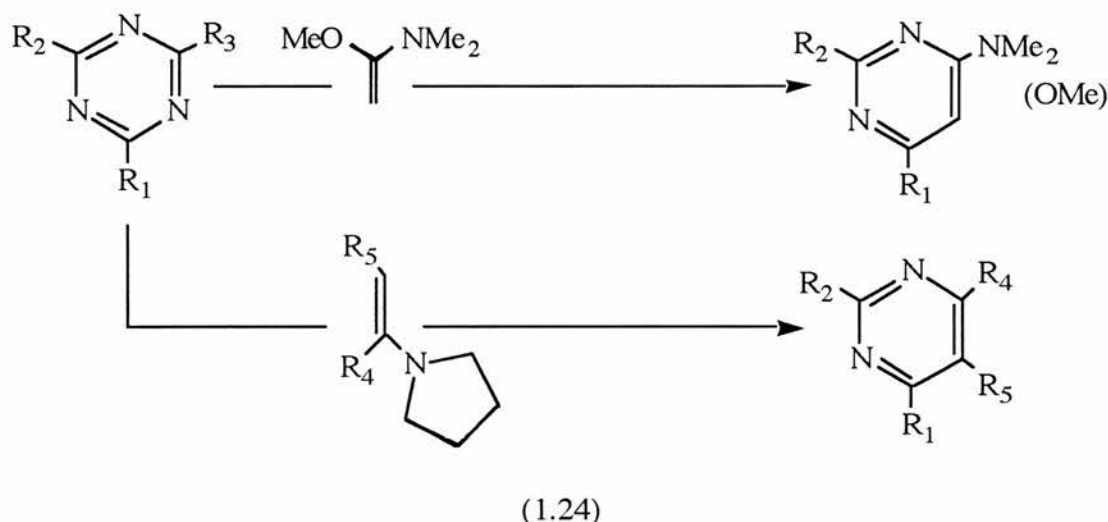
However, as seen previously for the diazines, such reactivity does not preclude the possibility of 1,3,5-triazines undergoing normal electron-demand Diels-Alder reactions (Fig. 1.25) with electron-deficient dienophiles[42].

(1.25)
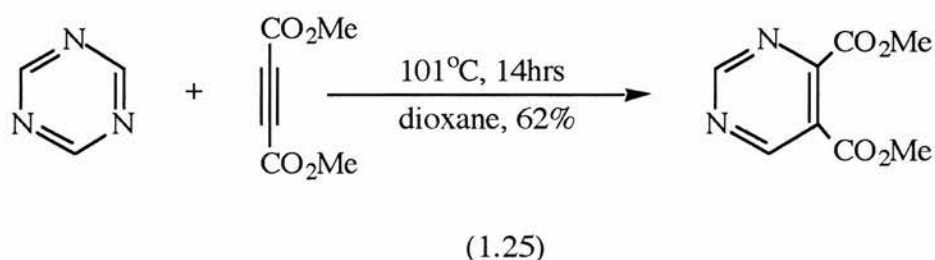
The recent successful preparation of 1,2,3-triazine and the subsequent study of its reactions with electron-rich dienophiles[44] (Fig. 1.26) has shown its potential for involvement in inverse-electron demand Diels-Alder reactions, with the mode of cycloaddition across the N-3/C-6 positions; the nucleophilic carbon of the dienophile attaches itself to C-6 of the triazine nucleus. Extrusion of molecular nitrogen from the

cycloadduct (and a subesquent expulsion from the enamine reaction) gives rise to substituted pyridines.

(1.26)
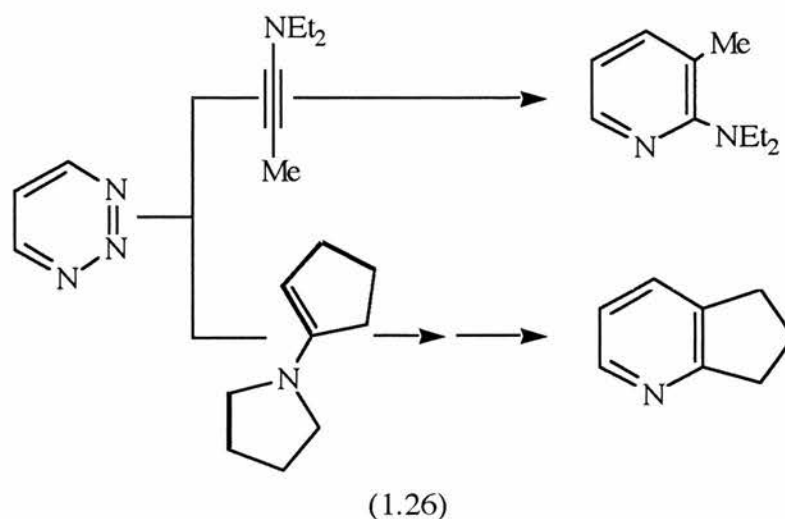
One of the most thoroughly investigated heterocyclic systems, with reference to 4π diene participation in the Diels-Alder reaction, are substituted 1,2,4-triazine systems (<u>as</u>-triazines)[45]. It is known that 1,2,4-triazine derivatives are electron-deficient azadienes, and as such, can be utilised in inverse electron-demand Diels-Alder reactions. Generally, the complementary addition of electron-withdrawing groups to the 1,2,4-triazine nucleus increases its rate of participation in inverse electron-demand Diels-Alder reactions, influences the mode of cycloaddition (C-3/C-6 vs. N-2/C-5) and determines the regioselectivity observed upon reaction, with the observed regioselectivity of the former mode being subject to triazine substituent control[46,47]. Moreover, Diels-Alder reactions of 1,2,4-triazines with electron-rich olefins are sensitive to the dienophile's reactivity[46,48,49].

An example of this is in the reaction of substituted 1,2,4-triazines with 1-ethoxy-1-(dimethylamino)ethylene (Fig. 1.27)[46]. The cycloaddition reaction occurring across the triazine nucleus at C-3/C-6 has a strong preference for attachment of the nucleophilic carbon of the dienophile to C-3 of the triazine[**A**], leading to the formation of substituted pyridines (via the expulsion of molecular nitrogen and methanol).

(1.27)
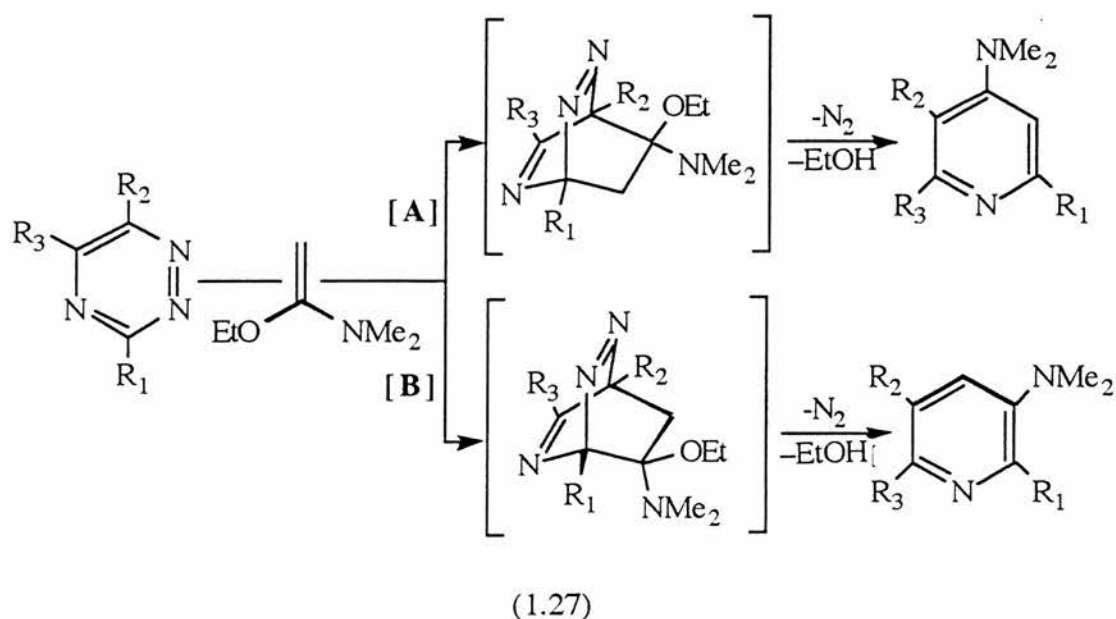
In summary, the reactions of substituted 1,2,4-triazines with electron-rich dienophiles, including O,O / O,S / O,N / N,S-ketene acetals, S,S-ketenethioacetals, N,N-ketene aminals, enol ethers, enamines and reactive or strained olefins have been studied to reveal the effects of electron-withdrawing groups, dienophile activity and substitution patterns/steric effects on the observed mode of cycloaddition and regioselectivity, and the results are generally in accordance with cycloaddition[46,47,50] across the C-3/C-6 positions of the triazine nucleus (Fig. 1.28).

As previously stated, the regioselectivity of the C-3/C-6 cycloaddition process is subject to control by the electronic and steric properties of the substituents on the 1,2,4-triazine, the electronic and steric parameters of the electron-rich dienophile, and the reaction conditions (such as polar vs. non-polar solvent)[45]. For such cycloadddition reactions, the nucleophilic carbon of the electron-rich dienophile has a strong preference for attachment to C-3 of the triazine nucleus (Fig. 1.28 [A]).

The complementary placing of additional electron-withdrawing substituents on the triazine nucleus (for example on C-6 or C-3/C-5/C-6) increases the rate of participation of the 1,2,4-triazine in cycloaddition reactions and can also enhance the observed regioselectivity. Moreover, the correct positioning of strong electron-

withdrawing substituents on the triazine nucleus (for example on C-3 or C-3/C-5) is sufficiently powerful to reverse the normal regioselectivity (Fig. 1.28 [B]) and serves to illustrate the regiocontrol available by careful selection and positioning of 1,2,4-triazine substituents[46,47]. In tandem with this, the electron-rich dienophile can alter or control the synthetic course of the cycloaddition reaction, with the more reactive electron-rich olefins undergoing reactions in mild conditions and with increased regioselectivity[47,51,52].

(1.28)
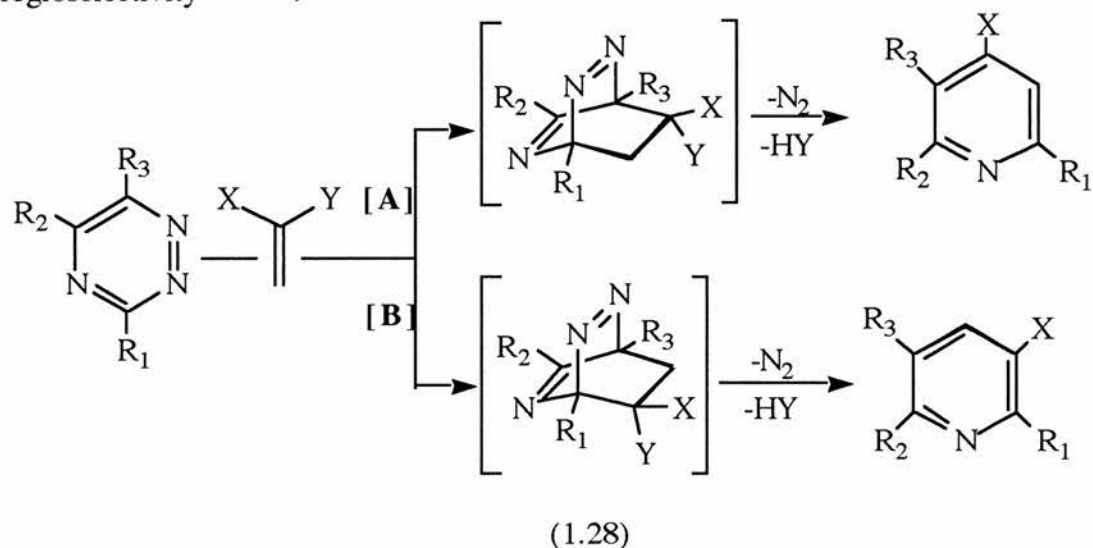
Alternatively, 1,2,4-triazine reactions with 1-(diethylamino)propyne can result in cycloaddition across N-2/C-5 or C-3/C-6 of the triazine nucleus[53]. The predominant cycloaddition mode is across the N-2/C-5 positions (Fig. 1.29), with attachment of the nucleophilic carbon of the ynamine to C-5 (Fig. 1.29 [A]).

(1.29)
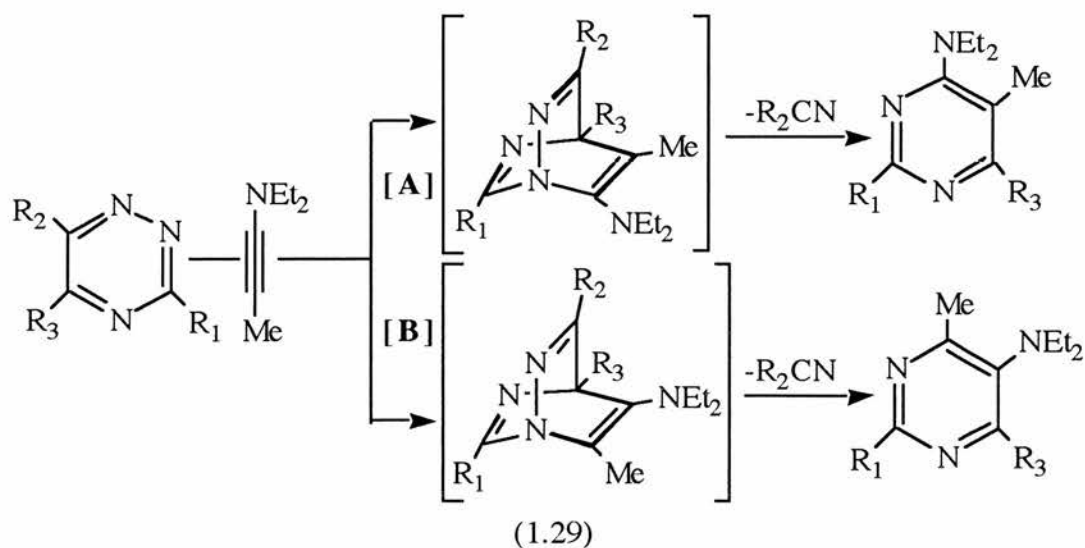
However, substitution at C-5 can result in a change of the cycloaddition mode, with addition of the ynamine across the C-3/C-6 of the triazine nucleus (Fig. 1.30).

(1.30)
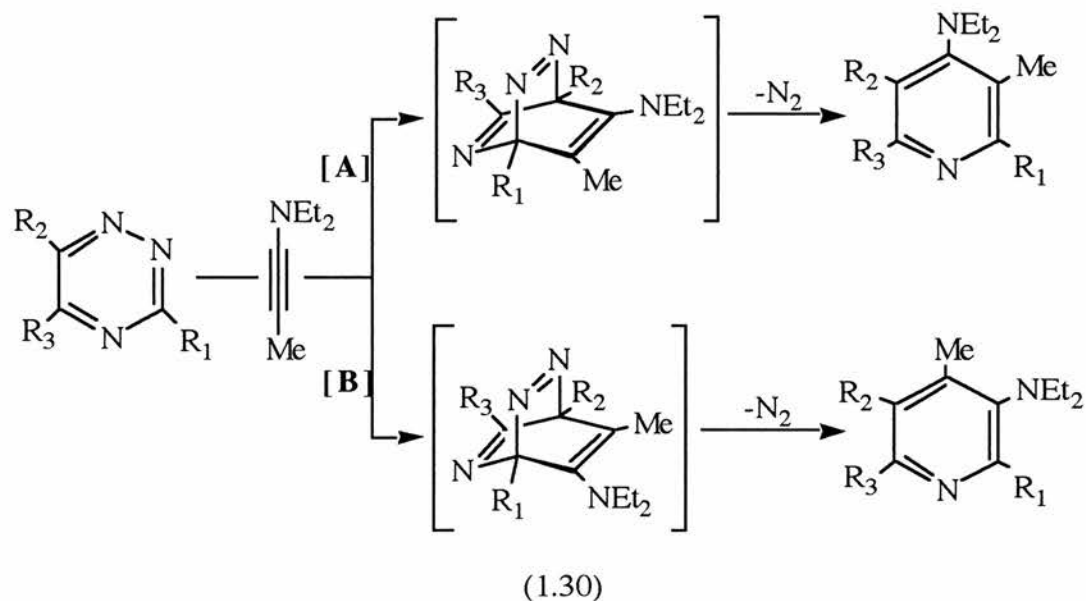
As previously stated, for such reactions, there is normally a strong preference for the nucleophilic carbon of the ynamine to be attached to C-3 of the 1,2,4-triazine nucleus (Fig. 1.30 [A]). However, the presence of electron-withdrawing substituents at C-3 or C-3/C-5 will control the observed regioselectivity for such cycloadditions.

As with all the heterocyclic systems previously discussed, 1,2,4-triazines are sufficiently reactive that participation in cycloaddition reactions with electron-deficient dienophiles is possible. Addition of strong electron-donating substituents to the triazine nucleus (-OMe, -NMe$_2$) increases the rate of participation of triazines in normal electron-demand Diels-Alder reactions[48,49].

When the triazines are fully substituted with electron-donating groups, the systems are sufficiently electron-rich to react with dimethylacetylenedicarboxylate[48] (Fig. 1.31). The reaction involves cycloaddition across the N-2/C-5 positions, yielding substituted pyrimidines after nitrile expulsion, whereas reactions of 1,2,4-triazines which are not fully substituted with electron-donating substituents with this alkyne forms pyrido-1,2,4-triazines and substituted vinylates[49].

$$R_1 = R_2 = R_3 = NR_2$$
$$R_1 = R_2 = NR_2 , R_3 = OMe$$

(1.31)
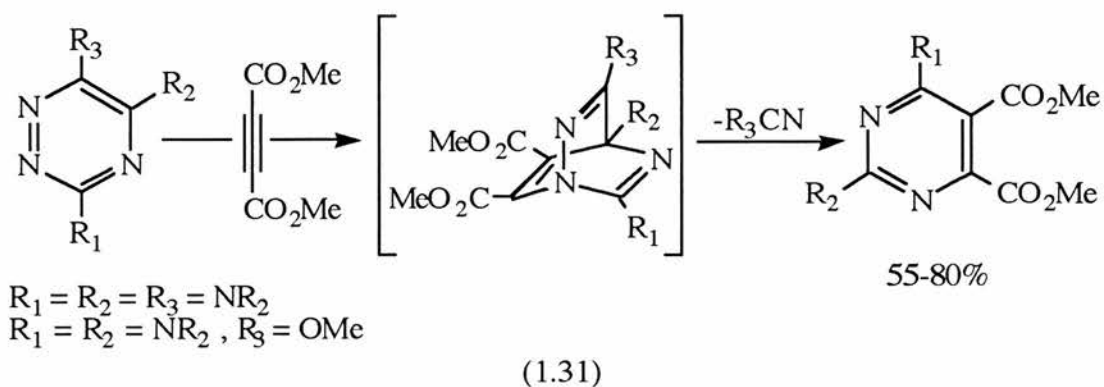
However, such addition of electron-donating substituents to the 1,2,4-triazine nucleus does not lessen their ability for utilisation in Diels-Alder reactions with electron-rich dienophiles. For example, triazines with electron-donating substituents can react with 1-(diethylamino)propyne[48], undergoing cycloaddition across either the C-3/C-6 or N-2/C-5 positions (Fig. 1.32), yielding either substitiuted pyridines or pyrimidines, with each distinct triazine substitution pattern having only one reaction product.

21-79%

86-91%

(1.32)
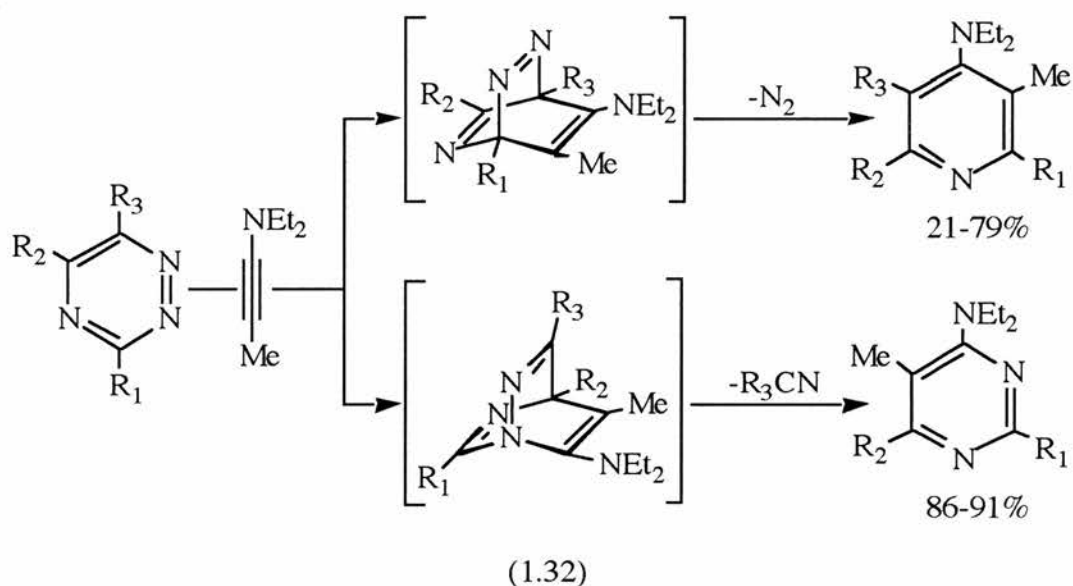
The last group of heterocyclic azadienes to be discussed in this section are the 1,2,4,5-tetrazines. This class of compounds is one of the most electron-deficient heterocyclic systems and reacts readily with all manner of multiply-bonded compounds in inverse electron-demand Diels-Alder cycloadditions[8,54]. The general reaction with olefins, first described by Carboni et al[55], involves cycloaddition across C-3/C-6, with

expulsion of molecular nitrogen leading to dihydropyridazine formation (Fig. 1.33). The reaction is facilitated by the addition of electron-donating substituents on the dienophile and electron-withdrawing substituents on the tetrazine.
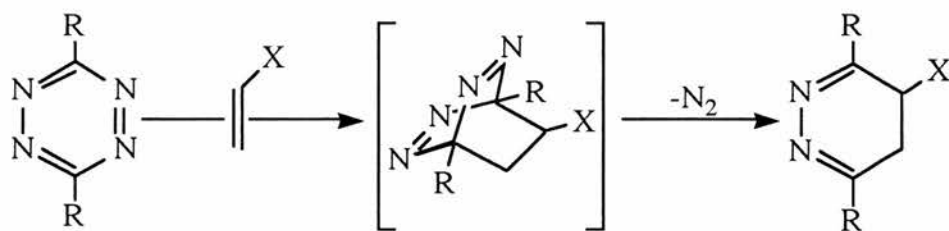
(1.33)

The dihydropyridazines formed in the reactions of tetrazines with olefins generally undergo oxidation easily in the reaction process by *in situ* aerial oxidation (by means of various oxidising agents) or with excess 1,2,4,5-tetrazine as the oxidant to form the corresponding pyridazine derivatives (Fig. 1.34).
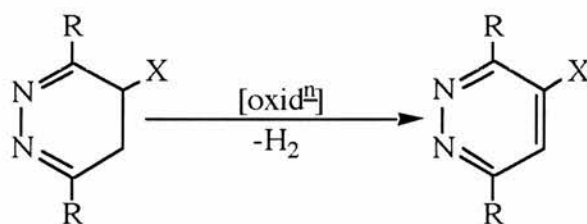
(1.34)

The olefin utilised can also affect the reaction pathway, with pyridazines being formed directly (without an oxidising agent) when the olefin used is a vinyl ether, enamine or an acetal (Fig. 1.35)[46a,e, 56].

$X = OR_1 , H$
$Y = OR_1 , N(R_2)_2$
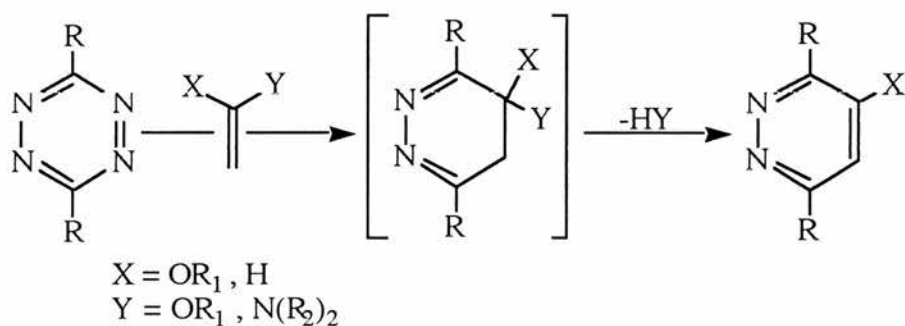
(1.35)

Similarly, the reaction of tetrazines with electron-rich alkynes under mild conditions leads to the aromatised pyridazines directly (Fig. 1.36). Again the cycloaddition occurs exclusively across the C-3/C-6 positions[56b, 57].

(1.36)
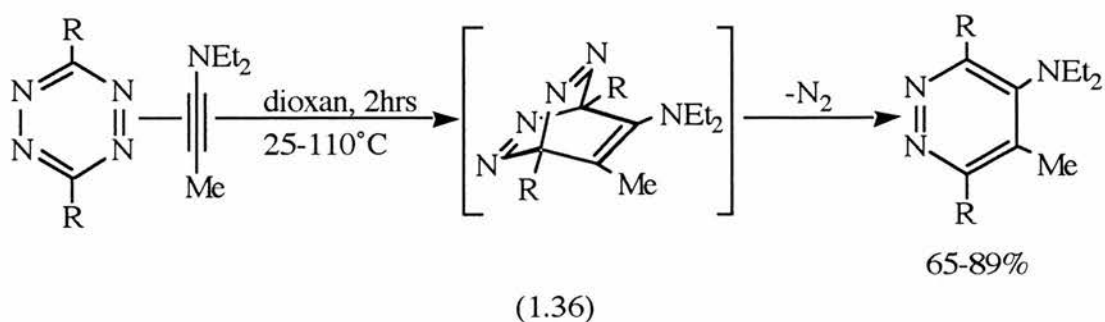
The Diels-Alder reaction of unsymmetrical and electron-deficient tetrazines with electron-rich dienophiles has been studied[46e,f, 58], and in the few reactions undertaken, the reactants participate in predictably regioselective cycloadditions across C-3/C-6 of the tetrazine nucleus, giving substituted pyridazines as products (Fig. 1.37), with each distinct dienophile substituent pattern leading to only one product.

X = OEt , NMe$_2$
Y = OEt , SMe , NMe$_2$

(1.37)
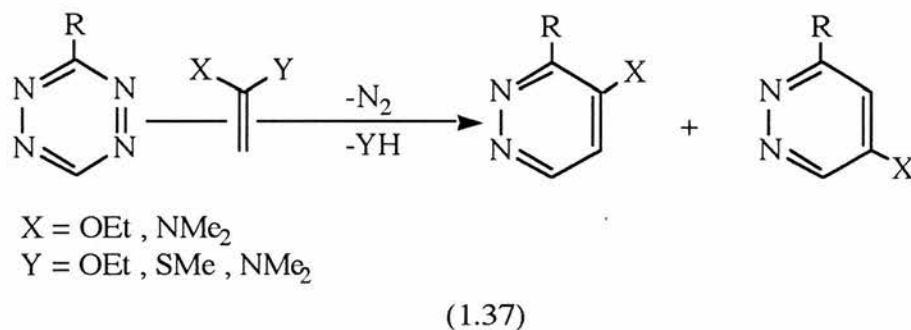
It must be noted that for all the nitrogen-containing heterocyclic systems that have been discussed, the Diels-Alder reactions have been of an intermolecular nature. What has not been touched upon so far is that most of these heterocycles can also undergo intramolecular Diels-Alder reactions[11].

These intramolecular cycloadditions are not only possible, but they have an additional incentive of a lowering of the entropic assistance needed for reaction to occur with the reacting functional groups (diene/dienophile) being incorporated in the same molecule. This translates into the reactions proceeding under milder conditions than for

their intermolecular counterparts, and also leads to the possibility of reactions proceeding which do not readily occur in an intermolecular context.

Various diazines have been studied for utilisation in intramolecular Diels-Alder cycloadditions. The reactions of variously substituted pyrimidinones incorporating alkenyl, alkynyl or nitrile dienophiles have been undertaken[41,59] (Fig. 1.38).

n = 3, 4
R = CH₃ , OH

(1.38)
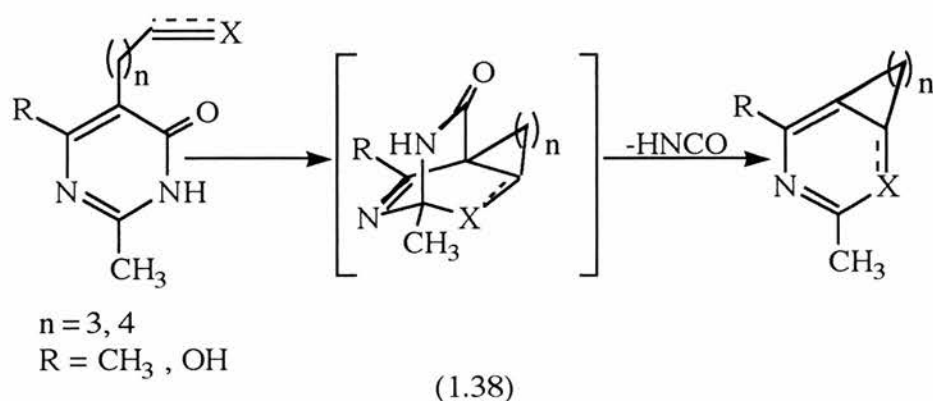
The mode of cycloaddition for these reactions, with dienophilic tethering at C-5, occurs exclusively across C-2/C-5. The products formed after cyanic acid expulsion from the cycloadduct can be bicyclic dihydropyridines, pyridines or pyrimidines (from alkenyl, alkynyl and nitrile dienophiles respectively).

For the pyridazines, intramolecular Diels-Alder reactions with unactivated and highly substituted alkenyl[60] (Fig. 1.39) and alkynyl[61] (Fig. 1.40) substituents have been investigated. In both cases, the tethering of the dienophile is at C-3 and the cycloaddition occurs across the C-3/C-6 position of the pyridazine nucleus.

Here, the length of the diene/dienophile tether is of great importance for the substrate interaction and product stability, with the optimal length being a three- or four-atom spacing between the interacting diene and dienophile in the molecule. As is seen, the initial cycloadduct expels molecular nitrogen, giving rise to substituted dihydrobenzenes for alkenyl substituents (Fig. 1.39), and directly to fully aromatic compounds for alkynylpyridazines (Fig. 1.40). For the alkenyl compounds (Fig. 1.39), aromatisation can occur after a secondary expulsion of hydrogen chloride.

X = H , alkyl , Hal , OR
R_1 , R_2 , R_3 = H , alkyl

(1.39)

X = NR_3
R_1 , R_2 = H, alkyl

7-80%

72-92%

(1.40)
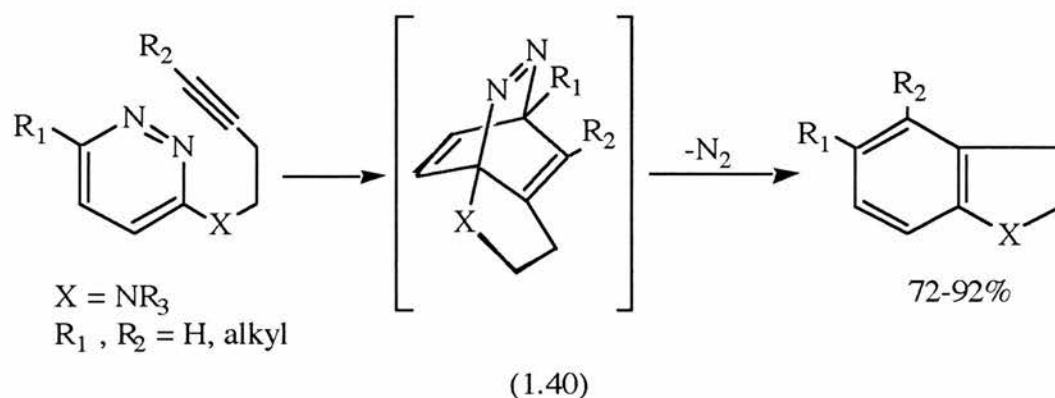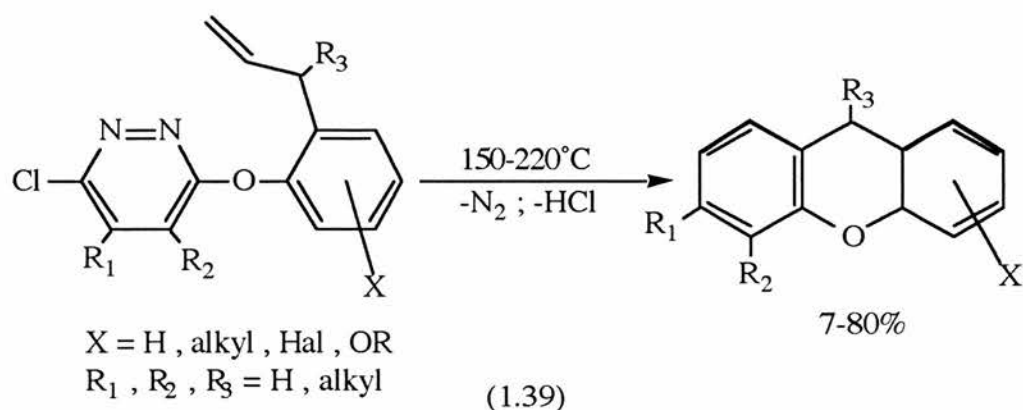
The utilisation of 1,2,4-triazines in intramolecular Diels-Alder reactions has been extensively studied. As before, there are steric constraints to be considered for intramolecular reactions undergone by these heterocycles. The reactions of alkynyl-triazines are interesting, as tethering of the dienophile to different positions of the triazine nucleus (C-3, C-5 or C-6) leads to different polycyclic reaction products. For reactions with tethering at the C-3 position[62] (Fig. 1.41), the mode of cycloaddition is across the C-3/C-6 of the triazine nucleus, and the expulsion of nitrogen leads directly to condensed pyridines.

n = 1, 2
X = S , O , NH
R_1 = R_2 = H, alkyl , Ar

(1.41)
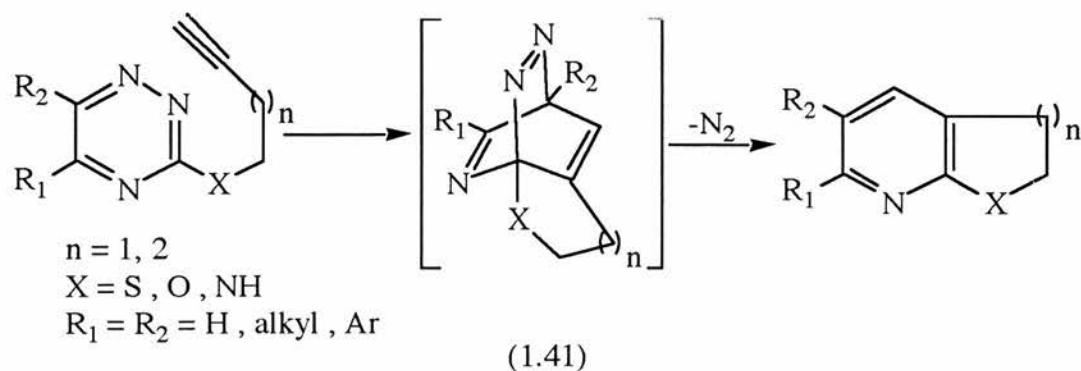
Similarly, for intramolecular reactions with the alkynyl substituent attached to the C-6 position[63] (Fig. 1.42), the mode of cycloaddition is again across the C-3/C-6 positions of the triazine nucleus, with condensed pyridines again being exclusively produced.

n = 1, 2
X = S , SO
R = alkyl , Ph

(1.42)
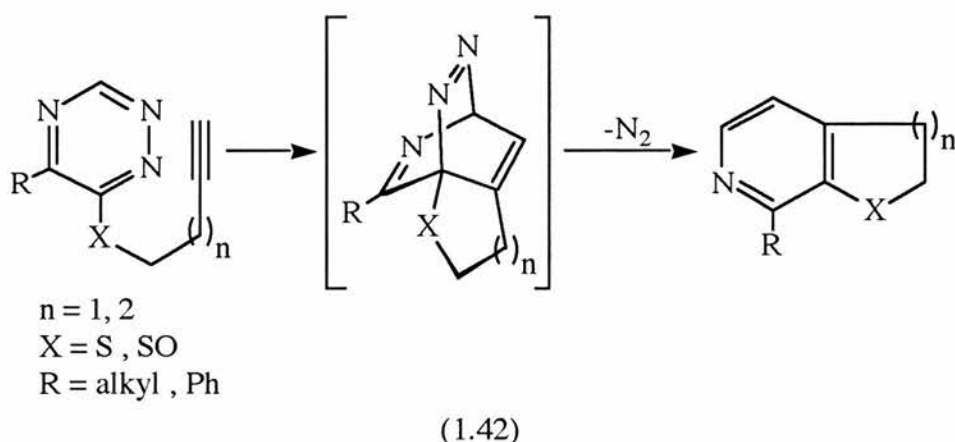
The main difference between the two reactions is the position of the nitrogen in the pyridine ring relative to the fused five or six-membered ring. This reaction scheme changes upon the tethering of the alkynyl substituent to C-5, with the mode of cycloaddition changing to across the N-2/C-5 positions of the triazine nucleus (Fig. 1.43). The expulsion of a substituted nitrile from the cycloadduct can lead to either condensed pyridazines or pyrimidines. The research[64] shows that the pyrimidines are formed exclusively for this class of compounds, but the reaction conditions required for reactions of this type are much more severe (several days' reaction at elevated temperatures).

X = N , O , S , CR$_2$
R$_1$ = SMe , Ar
R$_2$ = alkyl , Ph

(1.43)
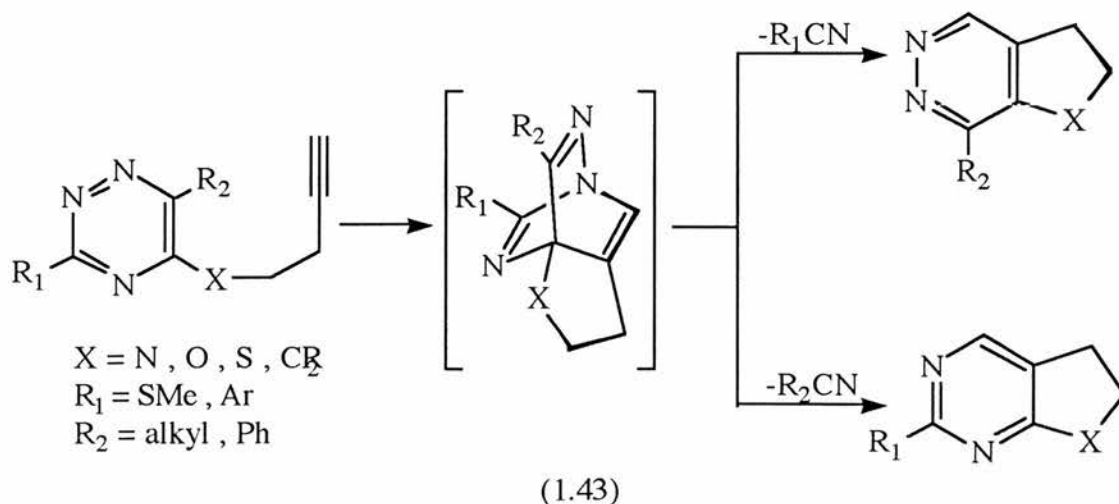
Alkynes are not the only triply bonded dienophiles which have been utilised; nitriles have been investigated[65] as the tethered dienophile in intramolecular Diels-Alder reactions with 1,2,4-triazines (Fig. 1.44). With the nitriles tethered at C-3 of the triazine nucleus, the mode of cycloaddition is the same as for the C-3-tethered alkynyl-triazines, namely across the C-3/C-6 positions of the triazine nucleus. As before, the extrusion of molecular nitrogen from the cycloadduct leads to the desired products, in these cases condensed pyrazines. The use of nitriles linked to the triazine through a sulphur atom has also been studied[65], with the reaction effectively being the aza-analogue of Figure 1.41 and leading to condensed pyrazines.

X = O , NHCOCF$_3$
R$_1$ = R$_2$ = H , Me , Ph

12-71%

(1.44)
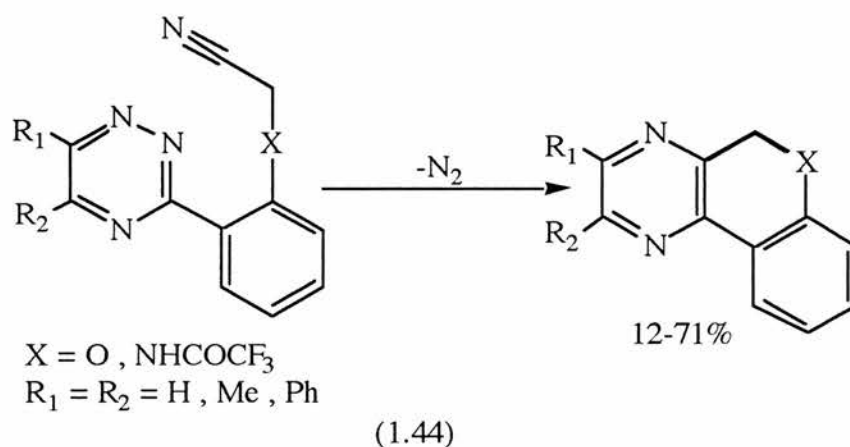
The last class of heterocyclic dienes to be considered for intramolecular Diels-Alder reactions are 1,2,4,5-triazines. Their utilisation in intramolecular cycloadditions with alkynyl substituents has been studied[66] (Fig. 1.45), with variation of both the heteroatom tethered to the tetrazine nucleus and the length of tether to which the dienophile is attached.

n = 2-5
X = SMe , SOMe , SO$_2$Me , NMe$_2$
Y = O , NH

(1.45)
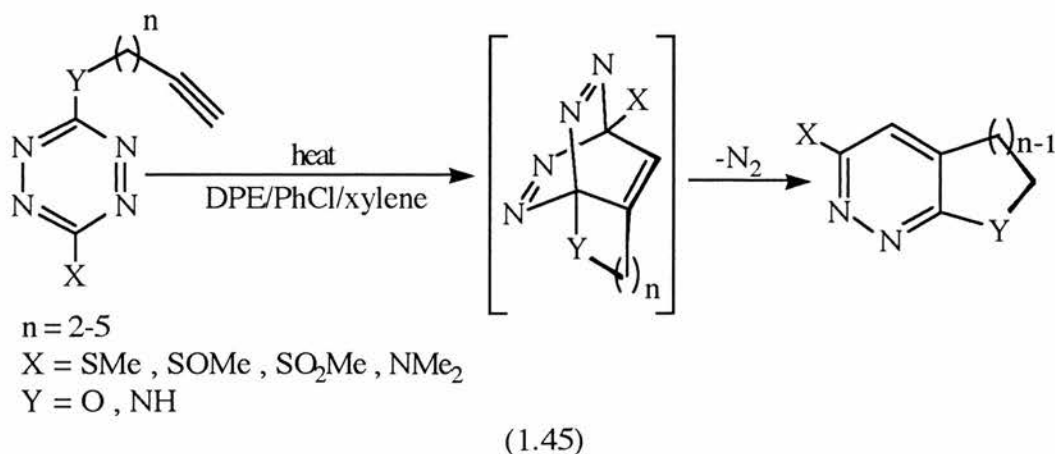
The mode of cycloaddition is across the C-3/C-6 positions, with extrusion of molecular nitrogen from the cycloadduct to give the condensed pyridazines.

So far, all of the cycloadditions considered have been Diels-Alder reactions of a monocyclic diene and a mono-dienophile. The initial objective of the present work was to investigate the possibility of extending this type of reaction to the synthesis of polymers. Such a procedure could be undertaken in one of two ways:- (a) The intermolecular reaction of a bis-diene with a bis-dienophile would constitute a polymerisation in its own right. (b) The intramolecular variant would serve as a curing process for a pre-polymer containing the appropriate heterocyclic diene units with suitably tethered dienophiles.

Chapter Two

Results and Discussion

As has been demonstrated in the Introduction, the Diels-Alder reaction is a useful synthetic tool for realizing the formation of simple aromatic and heteroaromatic ring systems. However, examples of extension of such reactions to form polymeric materials have not been so prevalent, the reasoning being that as Diels-Alder reactions are reversible, the polymers formed by such methods are not likely to possess good thermal stability (on account of their tendency to undergo retro Diels-Alder reactions).

This problem can be overcome by application of the same principle previously discussed for simple ring systems, namely formation of a polymeric Diels-Alder adduct which then loses a small molecule (an irreversible reaction); this can then lead to conversion into a thermally stable aromatic (or heteroaromatic) material, giving a potentially reliable polymer-making process. It must be recognised, however, that the expulsion of a gaseous material in a polymer-forming process can lead to voids in the product, with the resulting loss of overall mechanical performance.

(2.1)
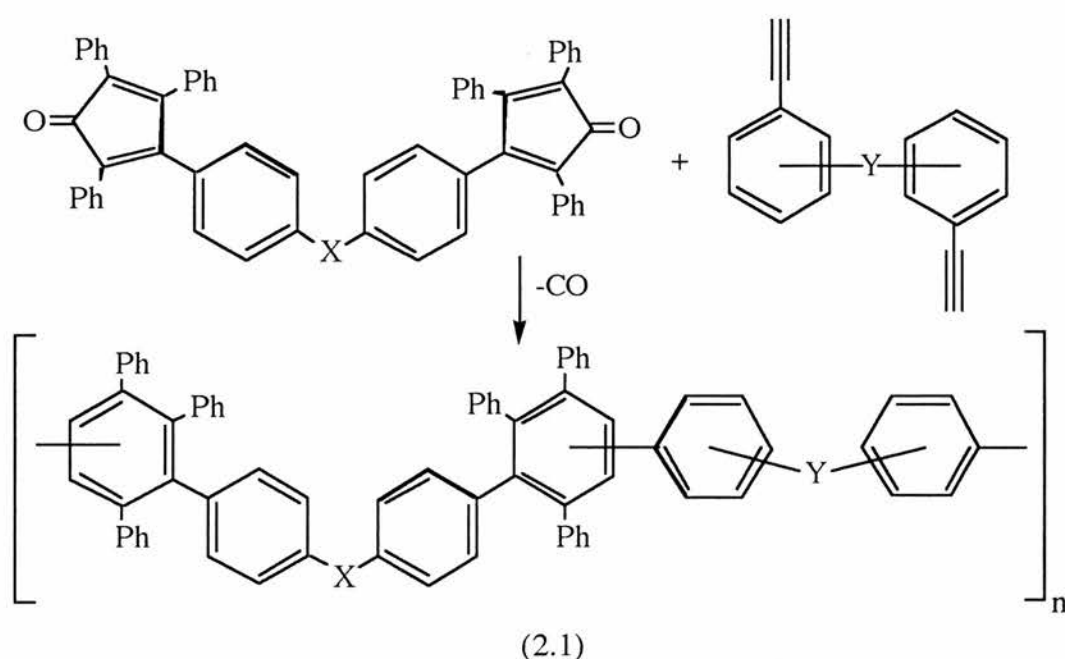
The use of a double Diels-Alder reaction to form such aromatic polymers has been explored[67,68], with utilisation of bis-tetracyclones (Figure 2.1) and bis-α-pyrones (Figure 2.2) in reactions with bis-alkynes producing the desired polymeric materials. As can be seen from both figures, the accompanying expulsion of carbon monoxide or carbon dioxide ensures an irreversible reaction.

(2.2)
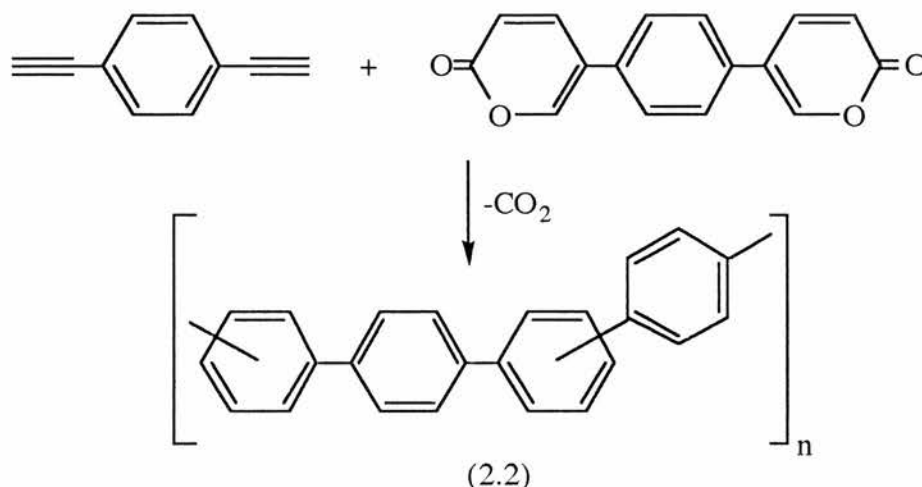
Use of bis-tetracyclones as bis-dienes has been more thoroughly investigated, as bis-tetracyclones are accessed more easily than bis-α-pyrones; the resultant aromatic polymers have good thermal stability in air at elevated temperatures ($>400°$C) and good solubility characteristics. The drawbacks of these compounds are their rapid decomposition above $500°$C (with accompanying release of volatile benzene and biphenyl[67b]) and the associated problems of charring and cross-linking at elevated temperatures. These problems all contribute to reducing their applicational usefulness (for example, their uses in non-flammable materials are limited).

As seen, a double Diels-Alder reaction works for aromatic polymer formation, but the current research is focussed on a feasible procedure for formation of heterocyclic polymers, using a similar approach, but with bis-azadienes. Although there are numerous examples in the literature of incorporation of azadienes into polymer chains (for example 1,3,5-triazine-containing polymers), to our current knowledge there is no record of the utilisation of the Diels-Alder reaction with bis-azadienes and

bis-dienophiles, with accompanying small molecule expulsion from the cycloadduct, as a curing procedure to yield stable heterocyclic polymers.

The previously recorded heterocyclic polymers generally have azadienes incorporated into the polymer chain by:-

(1) Preformed azadienes undergoing nucleophilic substitution.

(2) Formation of the azadiene as the polymerisation step.

An example of method (2) is the formation of some poly(arylene-1,2,4-triazines) by reaction of bis-(1,2-dicarbonyl) compounds with bis-amidrazones (Figure 2.3).

(2.3)
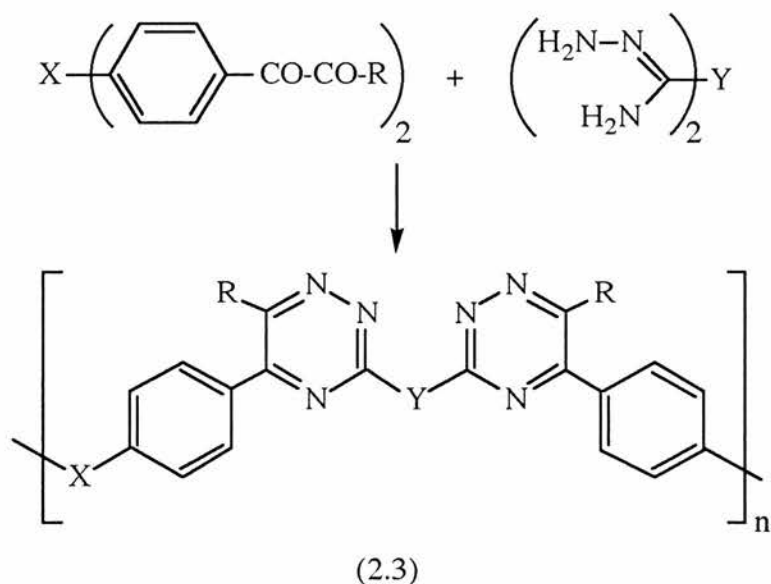
1,2,4-Triazines are among the most exhausively researched heterocycles, in respect of Diels-Alder chemistry[69], (cf. also pp.19-23 and 27-29 of Chapter 1), but apart from the above, there has been little recorded work on the formation and reactions of their bis-triazine counterparts. The approach used in this current investigation envisages **the use of various bis-1,2,4-triazines as the monomers**, with their subsequent Diels-Alder reactions as the polymerisation steps.

The various bis-triazines shown in Figure 2.3 are not particularly attractive in this respect, as even if the nature of the linkage Y is such that the triazine units are

spatially discrete, reaction of both rings with dienophiles might be subject to steric hindrance. Additionally, there is the possibility that cycloaddition across the N-2/C-5 positions would lead to nitrile elimination and chain cleavage.

It would therefore appear that the preferred mode of cycloaddition is across the C-3/C-6 positions, with the thermodynamically-driven elimination of molecular nitrogen from the cycloadduct leaving substituted pyridines. Sterically, at least, this mode of cycloaddition seems likely to be more favoured if the two triazine units in the monomer are linked through C-5, and attention has been concentrated on bis-triazines of this type. Two different synthetic pathways to such bis-triazines have been investigated:-

> (1) By constructing a triazine unit on each end of a suitably
> functionalised central core unit.
> (2) By preforming monotriazines and then either (i) coupling two
> differently functionalised triazines together or (ii) attaching one triazine
> to each end of a central core unit by a substitution type reaction.

These two pathways can be considered now in more detail. The first method of formation, namely the construction of a triazine unit on each end of a central core, can best be achieved by the reaction of bis-(1,2-dicarbonyl) compounds with semicarbazide derivatives. The formation of such tetracarbonyl compounds is of some interest as the reaction methods used for formation of the simple 1,2-dicarbonyl analogues cannot always be applied to these bis-functionalised compounds.

For example, one well-known method of formation for 1,2-dicarbonyls is the formation of benzoins and their subsequent oxidation to benzils (Figure 2.4). The initial step works well when the reaction involves the utilisation of one aldehyde only, and the primary problem is that when an unsymmetrically substituted benzoin is required, a mixture of different α-hydroxy ketones is likely to be obtained. The oxidation step can be undertaken using concentrated nitric acid or a copper(II) salt in air[70].

$$2 \quad Ar-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle H}{|}}{C}} \quad \xrightarrow{\text{KCN}} \quad Ar-\overset{}{\underset{\underset{\displaystyle OH}{|}}{CH}}-\overset{\overset{\displaystyle O}{\|}}{C}-Ar$$

$$Ar-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle O}{\|}}{C}-Ar \xleftarrow{} \quad \text{Oxid}^n$$

(2.4)
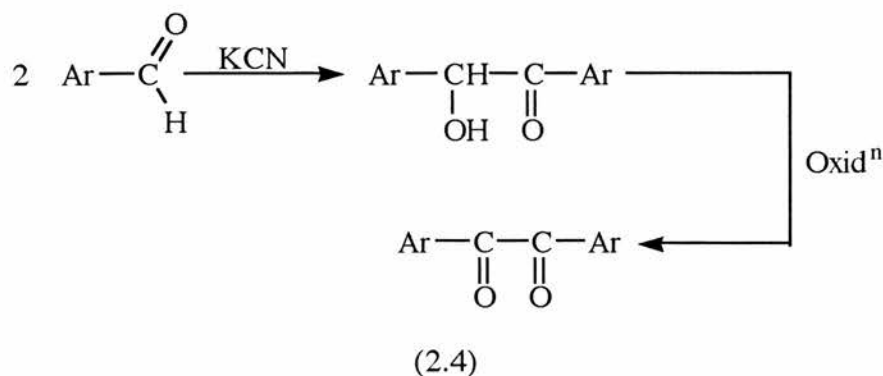
The formation of bisbenzoins is an unattractive option because of the need to use a dialdehyde and two molecules of monoaldehyde which can lead to mixtures of various α-hydroxy ketones.

The other classical method for formation of 1,2-dicarbonyls is the oxidation of CH_2CO- groups using selenium dioxide[71] (Figure 2.5). This reaction is attractive as it is more widely applicable to a variety of CH_2CO- groups, whereas the benzoin reaction is relevant almost exclusively for aromatic aldehydes. Although the selenium dioxide oxidation is a well-documented method, its problems include the toxicity of selenium and its compounds and the difficulty of freeing the product from elemental selenium, which tends to precipitate out of solution in finely divided state and varying colours, over prolonged periods of time. Therefore, the use of this method for tetracarbonyl compound formation on an industrial scale is not a commercially acceptable procedure.

$$O=Se=O \; + \; H_2O \; \rightleftharpoons \; O=Se\overset{\displaystyle OH}{\underset{\displaystyle OH}{<}}$$

(2.5)
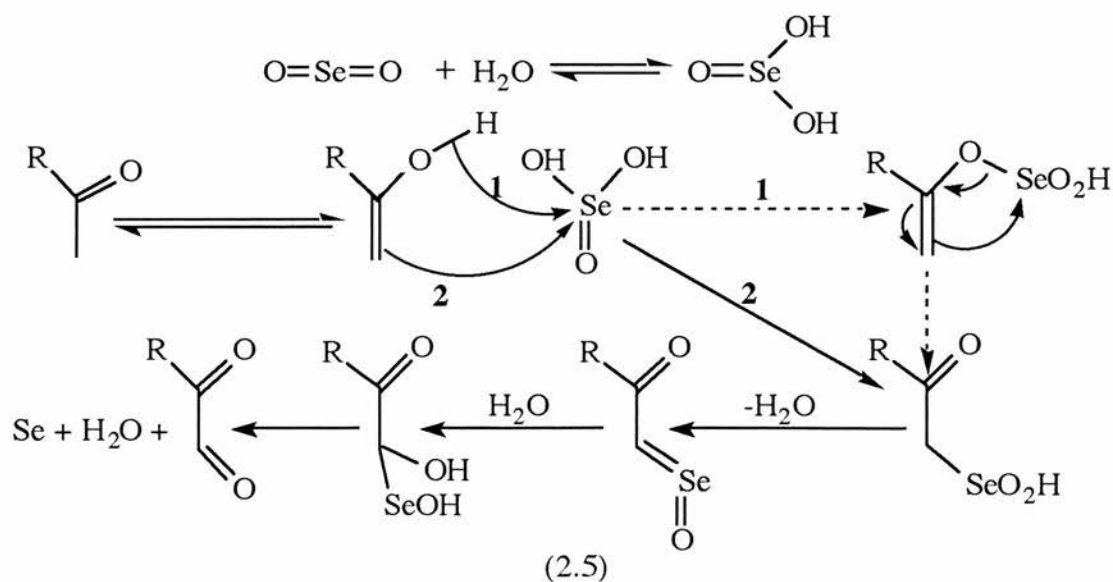
The formation of bis-(1,2-dicarbonyl) compounds by this route has been successful for a few cases[72], and the literature procedures have been repeated successfully (see p. 37), but on the whole the method has not been thoroughly investigated, due in part, to the inherent problems previously mentioned.

The oxidation of 1,2-dibromo compounds to the corresponding 1,2-diketones has been investigated[73], using aqueous dimethyl sulphoxide in the presence of hydogen bromide (Figure 2.6).

$$Ar-CHBr\text{-}CHBr-Ar \xrightarrow[110°C\;;\;4\text{-}8\;hrs]{DMSO\;;\;HBr\;;\;H_2O} Ar-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-Ar$$

(2.6)
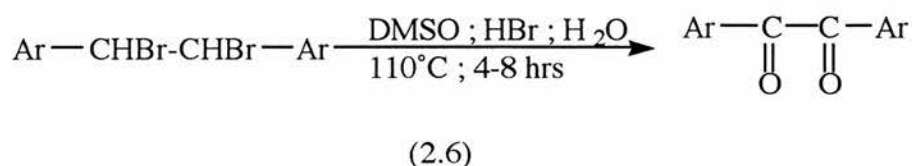
This research led to the use of substituted stilbenes[74] in a preparative process for 1,2-diketone formation (Figure 2.7). This again used dimethyl sulphoxide and hydrogen bromide for the conversion but no water was needed in the work-up. For some cases hydrogen peroxide was used to oxidise the hydrogen bromide, but in most cases the dimethyl sulphoxide itself fulfilled this role.

(2.7)
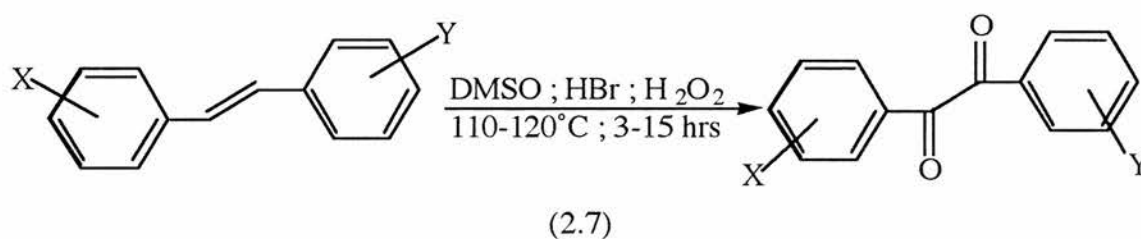
The oxidation of α-bromoketones to 1,2-diketones (or ketoaldehydes) may also be achieved by dimethyl sulphoxide[75]. Initial bromination of acetylbenzenes and their subsequent reaction with dimethyl sulphoxide forms the desired ketoaldehydes (also known as arylglyoxals) (Figure 2.8).

(2.8)
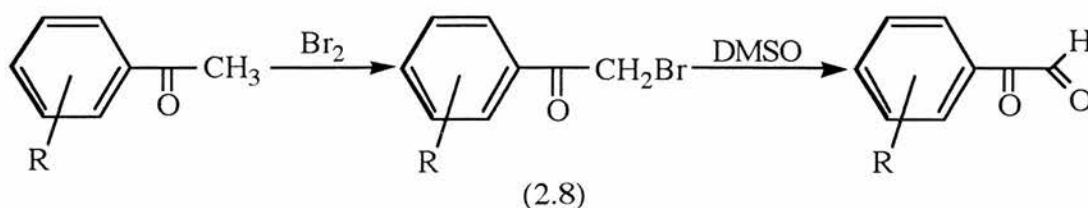
This is an attractive method for formation of bis-(1,2-dicarbonyl) compounds[76] as the initial diacetyl compounds are either commercially available or easily formed, usually by Friedel-Crafts acetylation, and the bromination is a simple literature procedure[72(a)]. Attempts were made to apply this method to the diacetyl compounds **1**, **2** and **3**, and although according to the literature the process works well, it was found that the desired products were not present in the quantities claimed. In fact only a trace of product could be detected by spectroscopic means, with the major proton resonances corresponding to unreacted starting material.

1

2

3

4

5

6
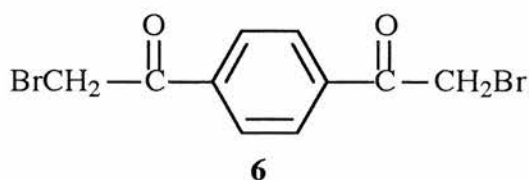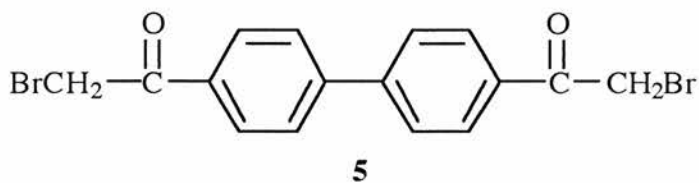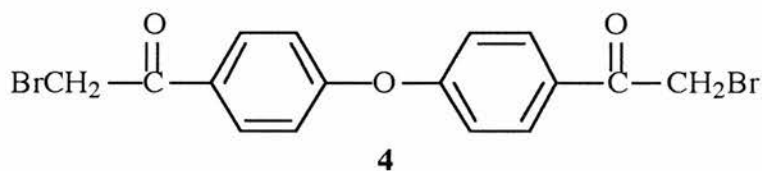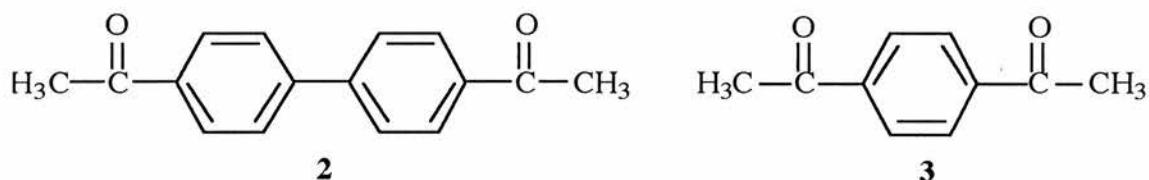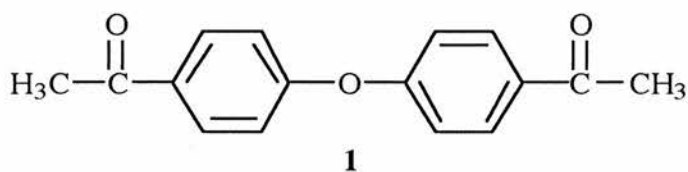
Concurrently, attempts were made to form bis-glyoxals from the bis-bromoacetyl compounds **4**, **5** and **6** using amine *N*-oxides in basic media as the oxidising agents[77] (Figure 2.9). Such amine *N*-oxides had previously been used to oxidise only monoketones.

$$2\,Me_3N^+\text{-}O^- \;+\; Ar(\text{-CO-CH}_2Br)_2 \longrightarrow Ar(\text{-CO-CHO})_2 \;+\; 2\,Me_3N^+HBr^-$$

$$(2.9)$$
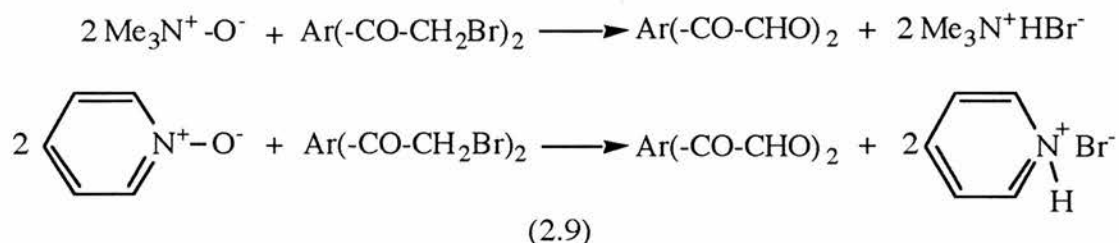
In attempts to apply the procedure to bis-(α-bromoketones), however, the products resulting from the use of both the trimethylamine- and the pyridine-*N*-oxides were not the expected tetracarbonyl products. In every case, and under a variety of reaction conditions, the products were very high-melting and very sparingly soluble in most common solvents. The explanation for this may be that in an alkaline environment, a rearrangement reaction analogous to the *benzil-benzilic acid rearrangement* can occur[78] (phenylglyoxal, for example, being known [78(a)] to undergo rearrangement, in presence of base, to mandelic acid), and this could lead to the bis-1,2-diketones (tetracarbonyls) which are formed undergoing rearrangement to give the salts of bis-α-hydroxy acids (Figure 2.10).

$$(2.10)$$
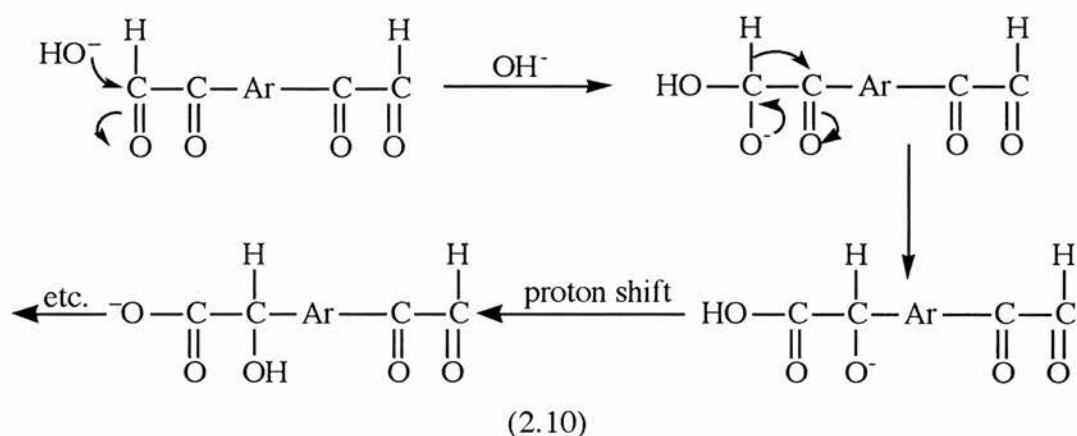
The successful synthesis of arylglyoxals and bis-glyoxals has been achieved in two ways from the corresponding acetyl- and diacetyl-aromatic compounds:

(1) using selenium dioxide (cf. p. 34);

(2) using hydrobromic acid and dimethyl sulphoxide.

The procedure using selenium dioxide is the 'classical' method, but in these particular cases the products were formed in low yield, and the time necessary for their complete purification rendered this route impracticable. The HBr/DMSO method is essentially a 'one-pot' alternative to the reaction shown in Fig. 2.8, the attraction being that isolation of the highly reactive brominated intermediates, e.g. **4-6**, is unnecessary. The procedure had been previously described[79] for the oxidation of certain acetophenones to arylglyoxals, and was successfully adapted for compounds **7-10** shown in Fig. 2.11.

$$X-C_6H_4-\underset{O}{\overset{\|}{C}}-CH_3 \longrightarrow X-C_6H_4-\underset{O}{\overset{\|}{C}}-\underset{O}{\overset{H}{\underset{\|}{C}}} \cdot H_2O$$

7: X=H **10** X=OH
8 : X=NO$_2$ **11** X=NHAc
9 : X=Br

13: X=H **16** X=OH
14: X=NO$_2$ **17** X=NHAc
15 X=Br

$$H_2N-C_6H_4-\underset{O}{\overset{\|}{C}}-CH_3$$

12

$$H_2N-C_6H_4-\underset{O}{\overset{\|}{C}}-\underset{O}{\overset{H}{\underset{\|}{C}}}$$

18

(unstable: would undergo
self-polymerisation)
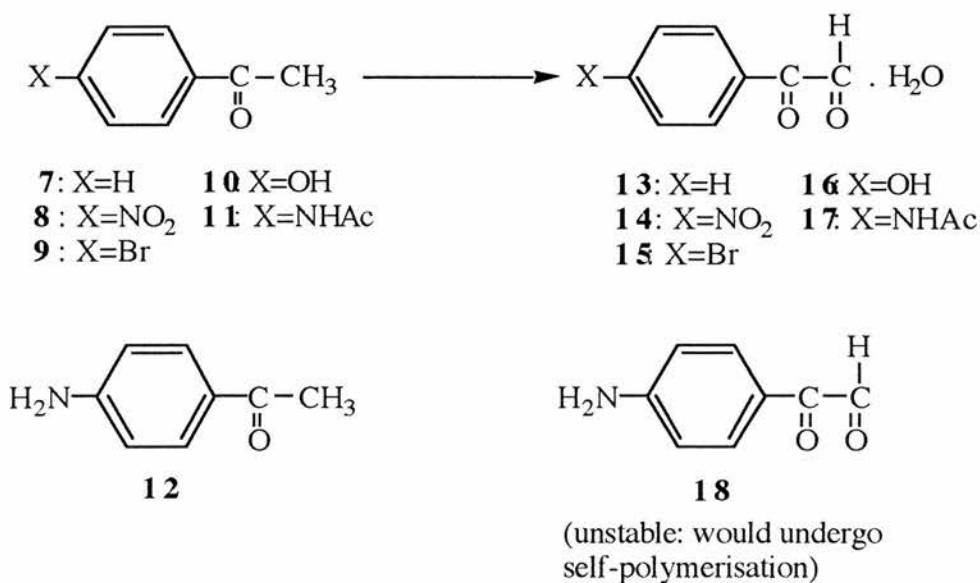
(2.11)

The formation of the acetamido-substituted glyoxal **17** could not be done in acidic media, as there would also have been hydrolysis of the acetamido group in the starting material, and in any deprotected glyoxal formed (e.g. **18**) the carbonyl group(s) would be expected to react with the free amino function released; so this glyoxal **17** was prepared by initial reaction of *p*-aminoacetophenone **12** with acetic anhydride and subsequent oxidation by the classical selenium dioxide method.

The HBr/DMSO method was then used successfully to oxidise the diacetyl compounds **1-3** (Fig. 2.12), the bis-glyoxals **19**, **20**, and **21** being obtained by a simpler work-up, and in higher yield, than using selenium dioxide. This has become the method of choice for the synthesis of these compounds, and has now been used successfully by colleagues for the oxidation of several other diacetyl compounds.

CH$_3$CO— —O— —COCH$_3$ $\xrightarrow[\text{24 h, 55°C}]{\text{HBr, DMSO}}$

1

OHC–CO— —O— —CO–CHO . n H$_2$O

19

Similarly

CH$_3$CO— — —COCH$_3$ ⟶

2

OHC–CO— — —CO–CHO . n H$_2$O

20

CH$_3$CO— —COCH$_3$ ⟶ OHC–CO— —CO–CHO . n H$_2$O

3   **21**

(2.12)
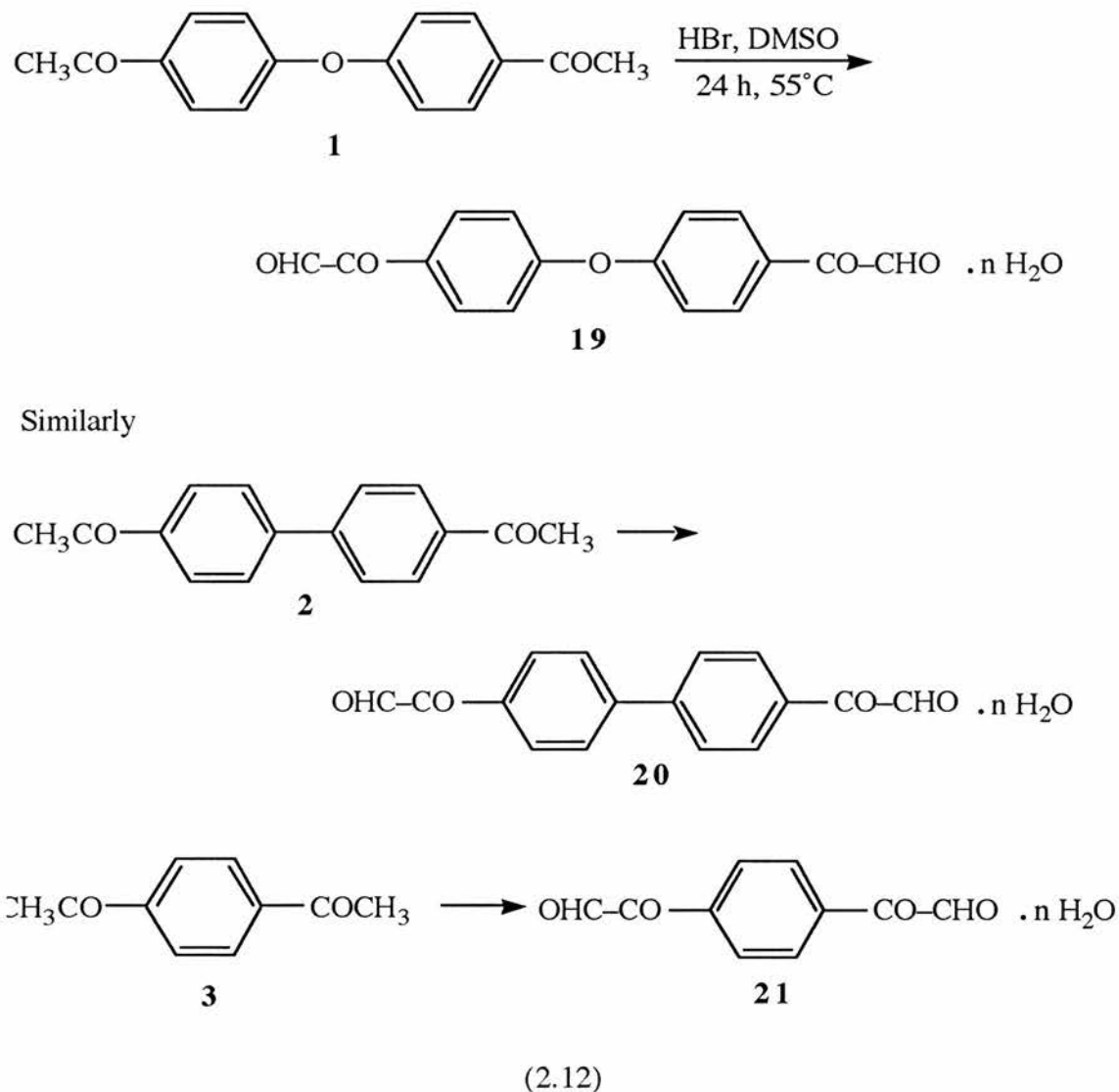
The only drawback in this procedure is the evolution of gaseous hydrogen bromide and dimethyl sulphide, and traces of the latter being left in solution. These problems can be overcome by trapping any volatiles evolved, and upon precipitation of the desired products a wash with aqueous sodium hypochlorite (10%) is advantageous.

The glyoxals and bis-glyoxals formed by this procedure were obtained in hydrated form, as evidenced by the 'formyl' proton resonance at ca. δ 6 [$-CH(OH)_2$] compared with the normal aldehydic chemical shift of $\delta \geq 10$. The varying degree of hydration causes the observed melting points to differ unpredictably from the reported values in certain cases. The observed melting points also vary with the rate of heating: the almost colourless hydrates lose water gradually upon heating, giving the yellow unhydrated aldehydes, and the melting points observed may be those of mixtures of hydrated and unhydrated forms.
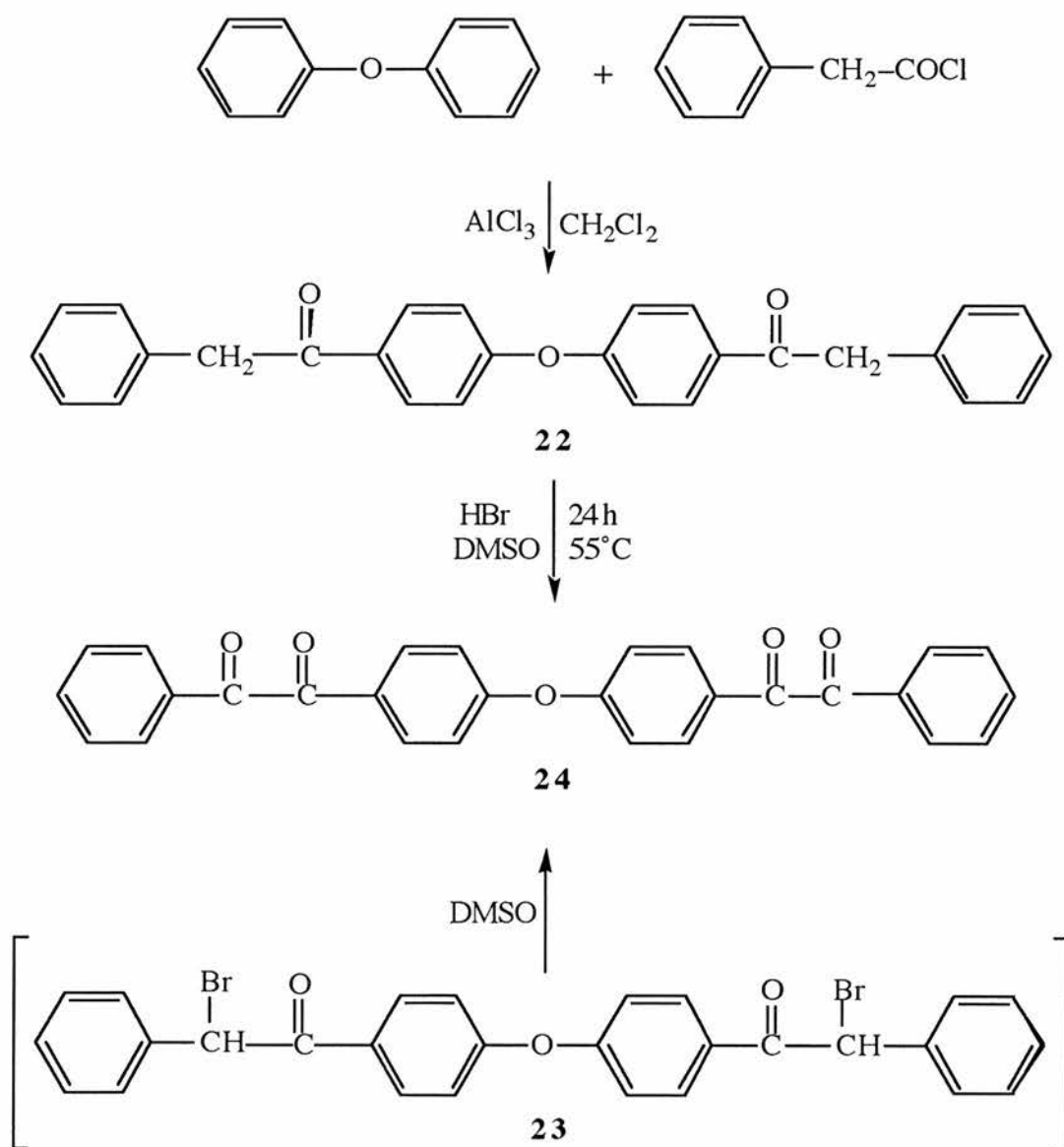
(2.13)

The HBr/DMSO method may also be used to produce bis-(1,2-diketones). Oxidation of bis-(p-phenylacetyl)phenyl ether, **22**, to p, p'-oxydibenzil, **24**, has previously been achieved using selenium dioxide[80]. The two-step procedure of Fig. 2.8, which involves the isolation of the dibrominated intermediate **23**, is unsatisfactory because of difficulties in purifying the latter, an acute lachrymator. The 'one-pot' alternative, however, shown in Fig. 2.13, produces the oxydibenzil **24** in 38% yield, and under less severe reaction conditions.

The formation of mono- and bis-(1,2,4-triazines) from the corresponding mono- and bis-keto-aldehydes was achieved by reaction with S-methylthiosemicarbazide. This is obtained, as its hydriodide salt, in good yield, by methylation of thiosemicarbazide using iodomethane[81], and the free base is released *in situ* by the use of sodium hydrogen carbonate. S-Methylthiosemicarbazide was chosen over thiosemicarbazide or semicarbazide, as the use of either of the latter would necessitate a further methylation step; and additionally the use of thiosemicarbazide or semicarbazide in such situations may lead only to (thio)semicarbazones[82,83], and a separate cyclisation step may then be necessary (Fig. 2.14).
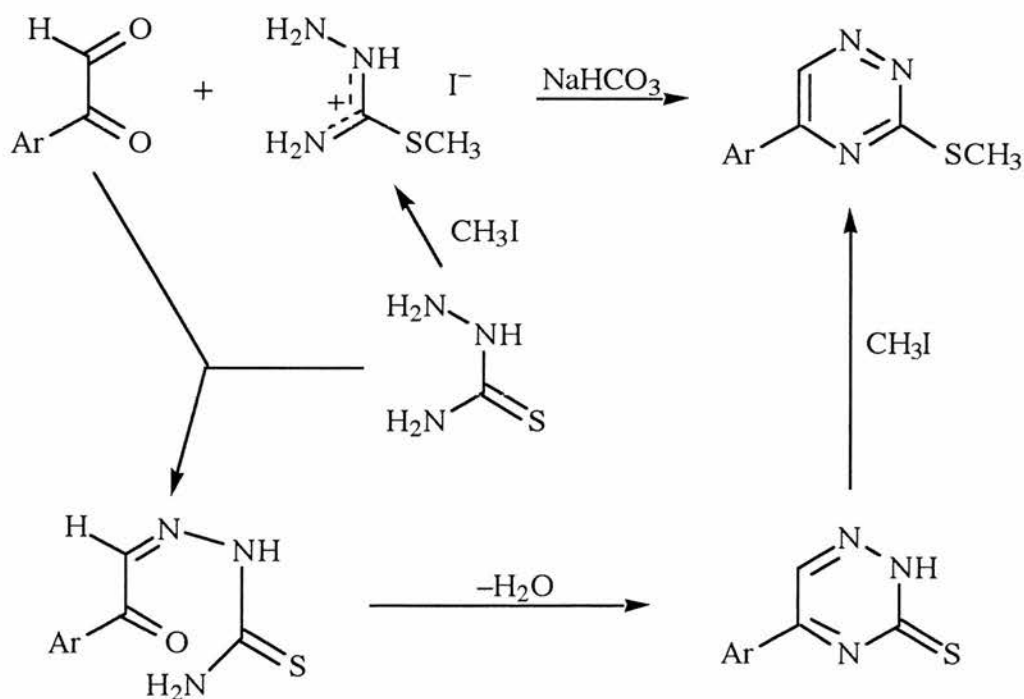
(2.14)

The methylthio substituent at C-3 of the triazine can then be easily oxidised, using reagents such as potassium permanganate or *m*-chloroperbenzoic acid, to the corresponding sulphoxide or sulphone. This oxidation has recently been achieved successfully by colleagues in the research group. All three substituents (sulphide, sulphoxide, and sulphone) serve as leaving groups in nucleophilic substitutions (sulphone being best), and the sulphoxide and sulphone serve to enhance the electron-deficient character of the triazine ring and hence increase the likelihood of participation in inverse electron-demand Diels-Alder reactions.

13 X=H
14 X=NO$_2$
15 X=Br
16 X=OH
17 X=NHAc

25: X=H   28 X=OH
26: X=NO$_2$ 29 X=NHAc
27 X=Br

19

30

20

31
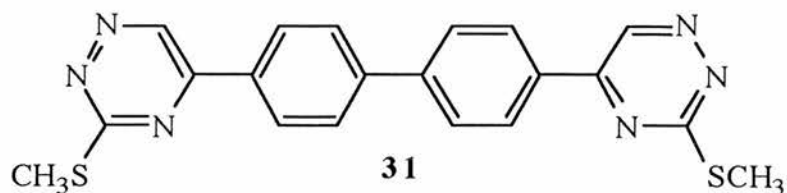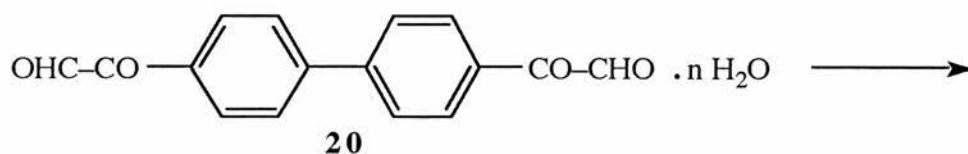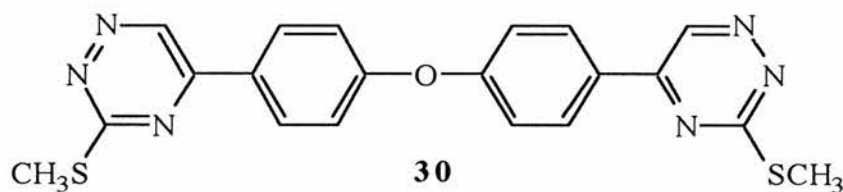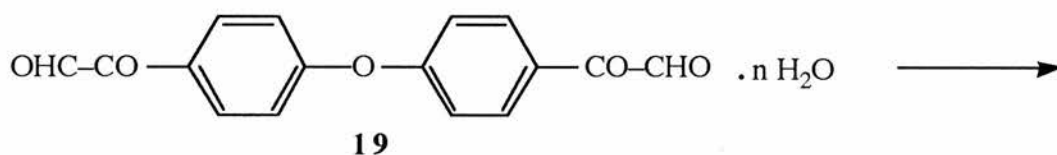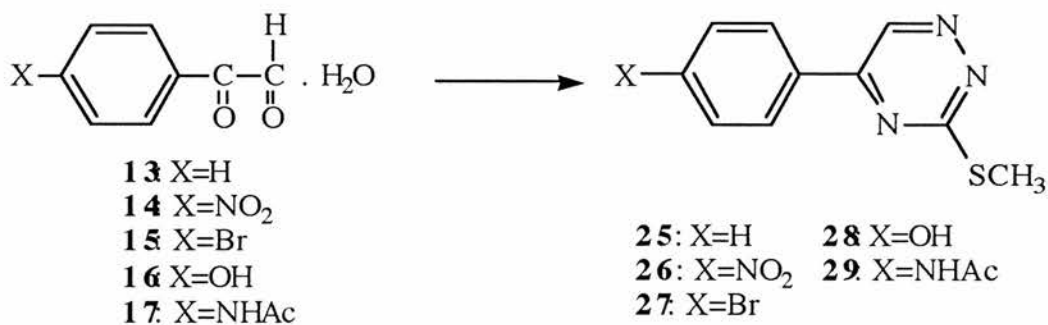
By the use of this cyclisation method, the mono-1,2,4-triazines **25-29** were synthesised in good yield and the bis-(1,2,4-triazines) **30** and **31** in low yield. As yet, the conditions for the syntheses of the bis-triazines have not been optimised: other representatives of this class of compound, prepared by colleagues in the group, were similarly difficult to obtain pure. Column chromatography was used, and the yields again were very low.
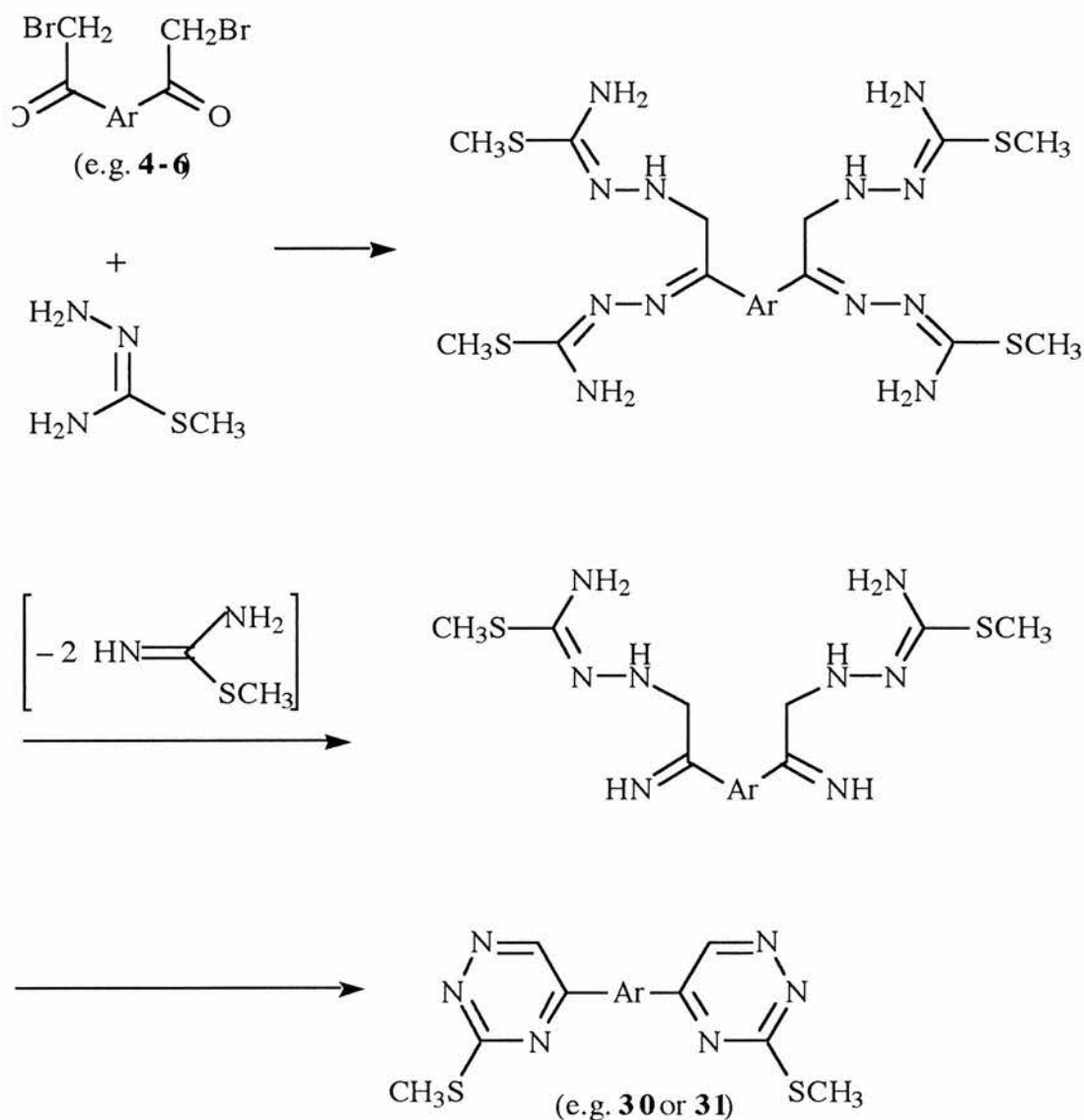
(2.15)

There is a possible alternative route[84] to the desired bis-triazines which would by-pass the tetracarbonyl intermediates altogether; this involves the reaction of *S*-

methylthiosemicarbazide with bis-(α-bromoketones), such as **4-6,** to give the bis-triazines directly. (The proposed sequence of steps[84] is shown in Figure 2.15, although others may be envisaged). This method was tried, but the reaction did not proceed as described in the literature; a viscous black product was obtained which was virtually insoluble in all the solvents tried. The reaction was repeated, varying the solvent system, but similar results were obtained.

Another way of approaching the synthesis of bis-(1,2,4-triazines) was by the attachment of one of the preformed monotriazines **25-29** to each end of a symmetrical core unit. The main intention was to use the functionality on the phenyl substituent of the monotriazine as the point of linkage to the central core unit. This approach was attempted using the sodium salt of 5-(p-hydroxyphenyl)-3-(methylthio)-1,2,4-triazine **28** with terephthaloyl and isophthaloyl chloride, in the expectation of obtaining the bis-triazines **32** and **33** (Figure 2.16).

32 : p-C$_6$H$_4$
33 : m-C$_6$H$_4$
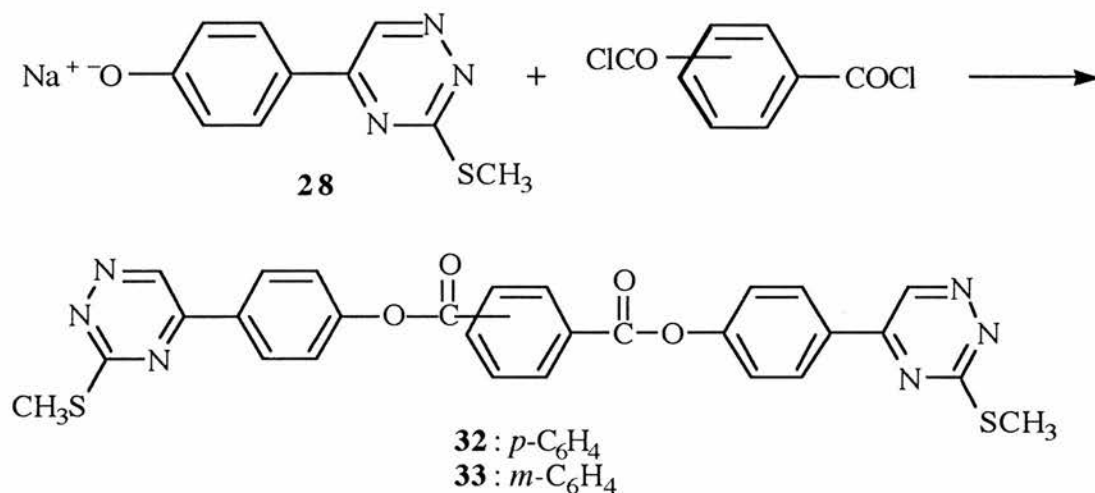
(2.16)

Once again this met with very limited success, and again the optimisation of reaction conditions has yet to be achieved. The attempted reactions with both terephthaloyl and isophthaloyl chloride at room temperature gave only unreacted triazine **28**, and in the former case elevation of the temperature gave a mixture of at least three products (by t.l.c.).

Another possible related method would involve utilisation of the *p*-aminophenyltriazine **34** (Figure 2.17) in reaction with terephthaloyl and isophthaloyl chloride. Attempts to form compound **34** by hydrolysis of the acetamido-compound **29** in basic media, however, were unsuccessful, at room temperature or on heating; the acetamidotriazine **29** was recovered unchanged.
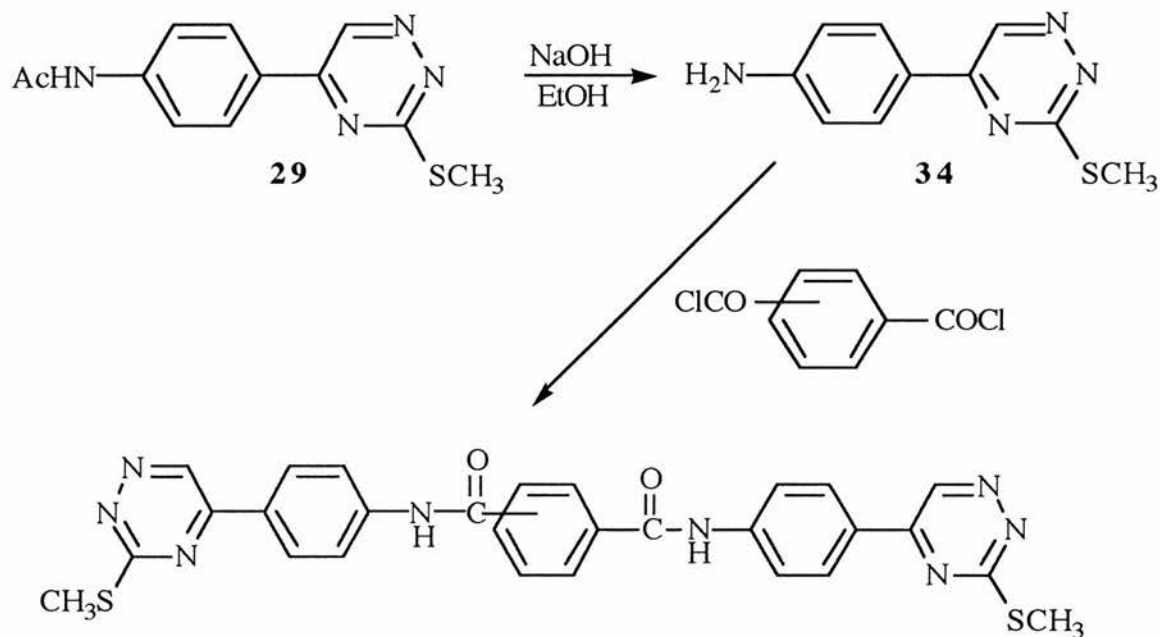
(2.17)

The successful synthesis of some bis-(1,2,4-triazines), potential bis-dienes for inverse electron-demand Diels-Alder polymerisations, led to attempts to form complementary bis-dienophiles. These attempts centred on two different compound types:-

(1) simple dialkynyl-aromatics;
(2) bis-(*o*-alkynylphenols).

The former were intended for simple intermolecular Diels-Alder reactions, and the latter for coupling through the phenol moiety to bis-triazines, with a subsequent

*intra*molecular Diels-Alder reaction (expelling molecular nitrogen) acting as a curing process (Figure 2.18; cf. Figure 1.41, p. 26).

(2.18)
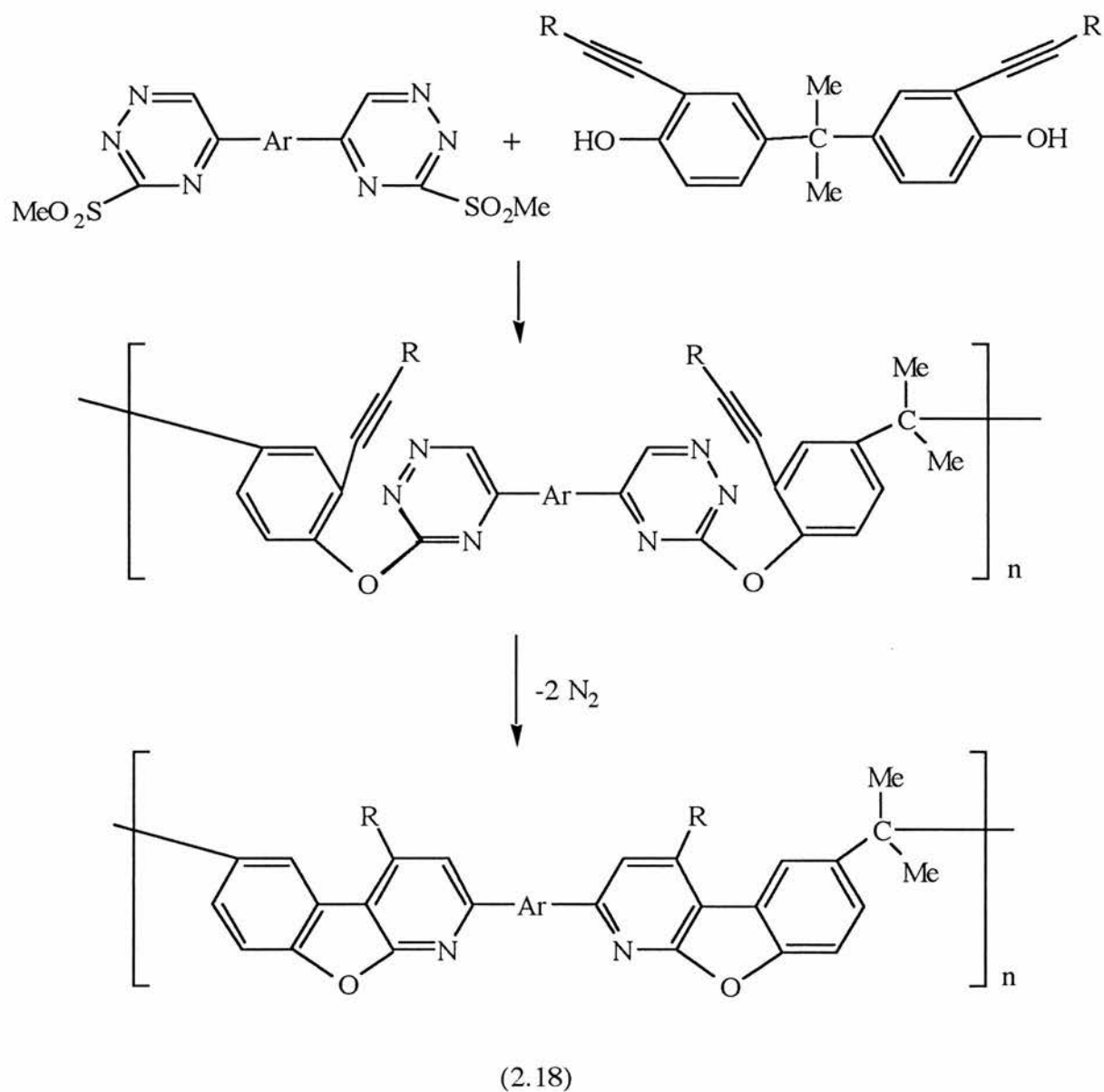
The simplest route currently available to diethynyl-aromatics was investigated within the group by Dr B.J.L. Royles[85]. This involves the same starting compounds, *viz.* diacetyl-aromatics, as are used for the synthesis of the bis-triazines. The diacetyl-aromatics **1**, **2**, and **3** are converted, by reaction with the Vilsmeier reagent (phosphoryl chloride and dimethylformamide) into bis-(β-chlorocinnamaldehydes), e.g. **35**, and these undergo base-induced elimination of formate and chloride ion to yield the bis-alkynes **36**, **37** and **38** (Figure 2.19).

The other type of bis-alkynes sought, *viz.* bis-(*o*-ethynylphenols), were more elusive. Bisphenol A, **39**, was chosen as the primary starting material, and this was converted into its dimethyl ether **40** by reaction with dimethyl sulphate in alkaline solution[86]. Friedel-Crafts acetylation of the latter, with aluminium chloride as catalyst[87], led to the diacetylated product **41**, but only to partial demethylation, and not complete demethylation as reported in the literature (Figure 2.20). The reaction was repeated, varying the solvent, and the proportion of demethylated product **42** increased; but the proportion of the dimethoxy-compound **41** was never less than 15%, and it was not considered advisable to proceed with attempts to react this mixture with a bis-triazine (thus forming a polymer) with such a high proportion of an unreactive impurity.
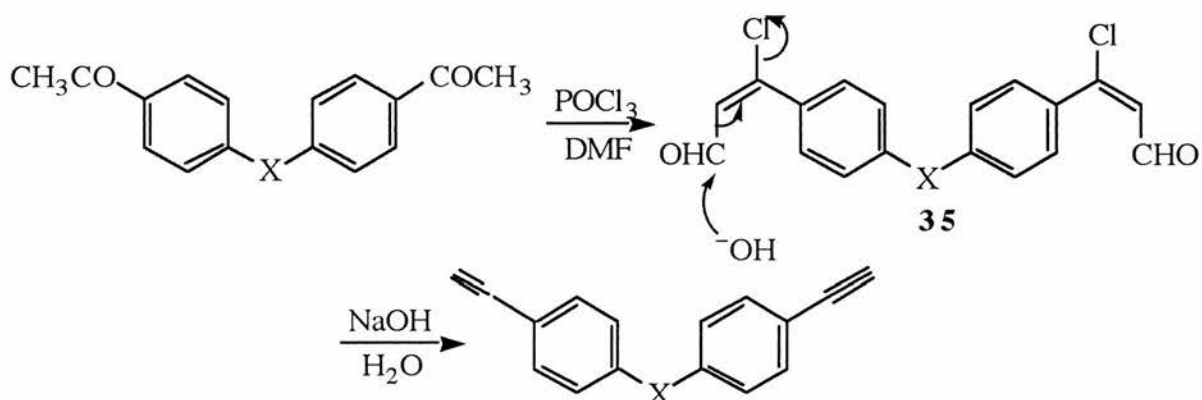
Thus
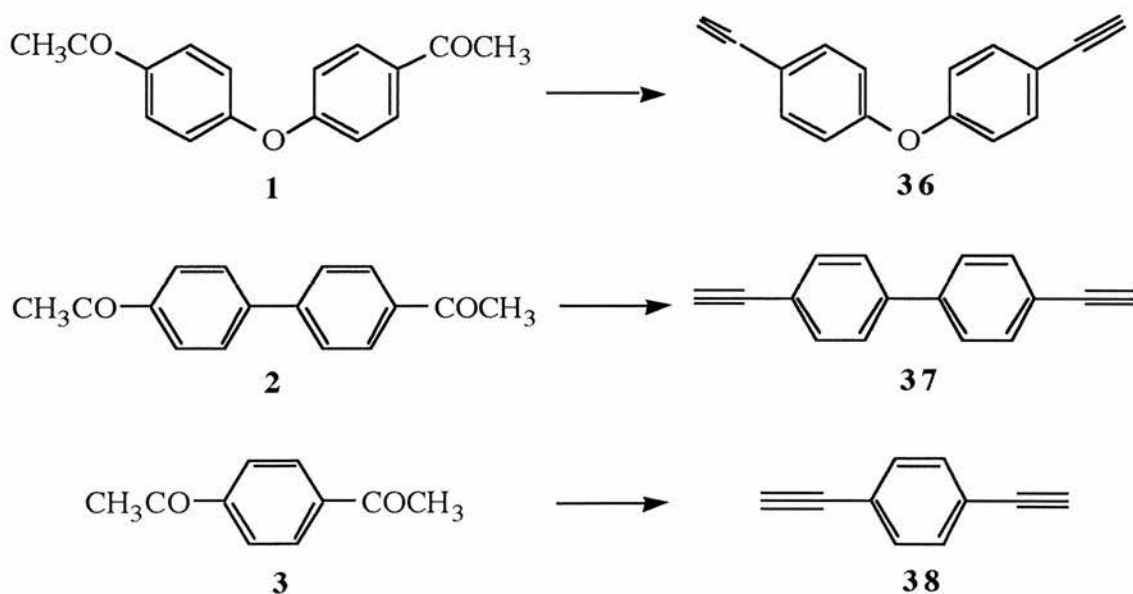
(2.19)
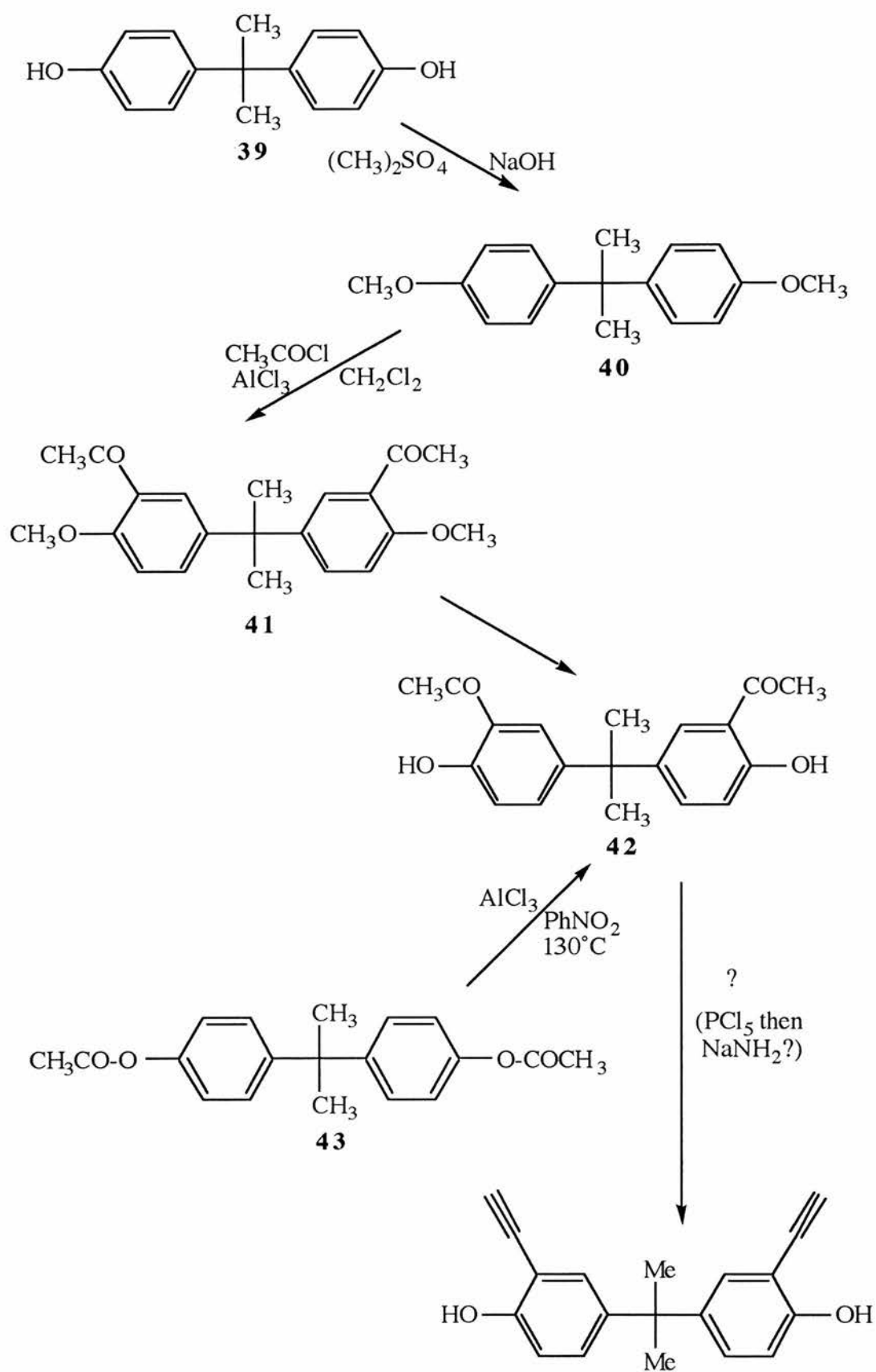
(2.20)

According to another literature report[88], compound **42** is also obtainable by the Fries rearrangement of bisphenol A diacetate, **43**, but this claim has not yet been investigated.

$$X-C_6H_4-Br \;(\text{or } I) \;+\; R-C\equiv C-H \;\xrightarrow[\;R_3N,\;CuI\;]{(Ph_3P)_2PdCl_2}\; X-C_6H_4-C\equiv C-R$$

39

Br$_2$

44

(protection of the OH groups may be required)

R

R

(2.21)
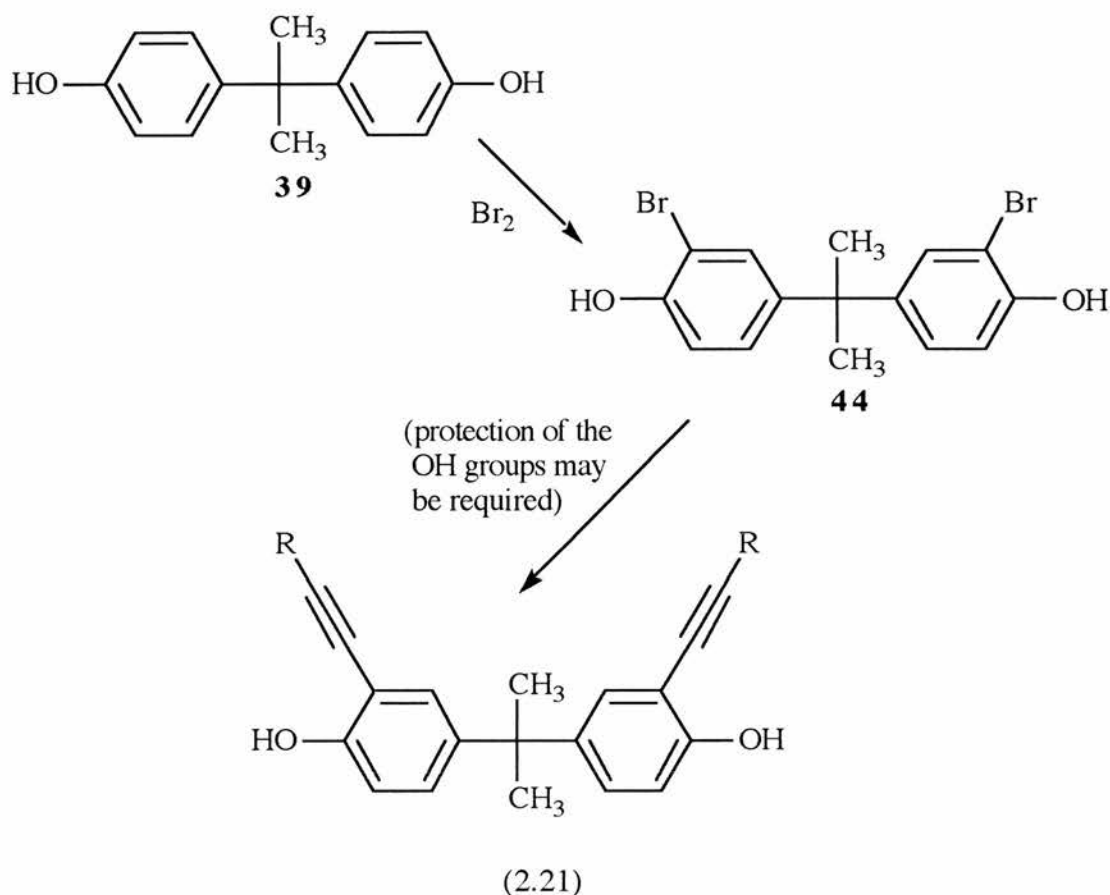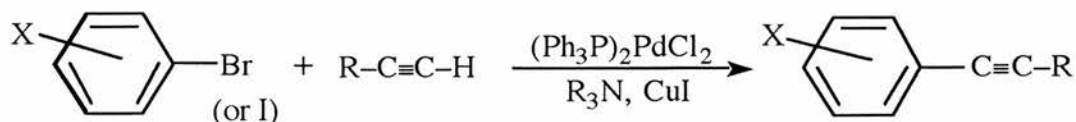
An alternative approach to a bis-(*o*-alkynylphenol), the early stages of which were investigated, might involve the palladium-catalysed coupling of a bis-(*o*-halogenophenol) with a simple alkyne[89] (Figure 2.21). Bromination of bisphenol A, using 2 molar equivalents of bromine[90], led to the bis-(*o*-bromophenol) **44**, but attempts by a colleague (G.A. McLean) to couple this dibromo compound with phenylacetylene failed[91], and alternative conditions for this coupling have not yet been investigated.

The second group of heterocycles investigated as possible bis-diene monomers was the 1,2,4,5-tetrazines. The incorporation of additional nitrogens into an azadiene system increases its electron-deficient character, and the diene is now expected to undergo cycloaddition more readily with electron rich dienophiles. The formation of 1,2,4,5-tetrazines, however, usually involves several steps in which the yields are generally poor. The tetrazine closest in character to the triazines studied here is 3,6-bis-(methylthio)-1,2,4,5-tetrazine **45**, the synthesis of which has been perfected by Seitz *et al.* in Marburg; a period of six weeks was spent by the author in Marburg in order to learn the preparative technique and to exchange ideas on possible future collaboration.

(2.22)
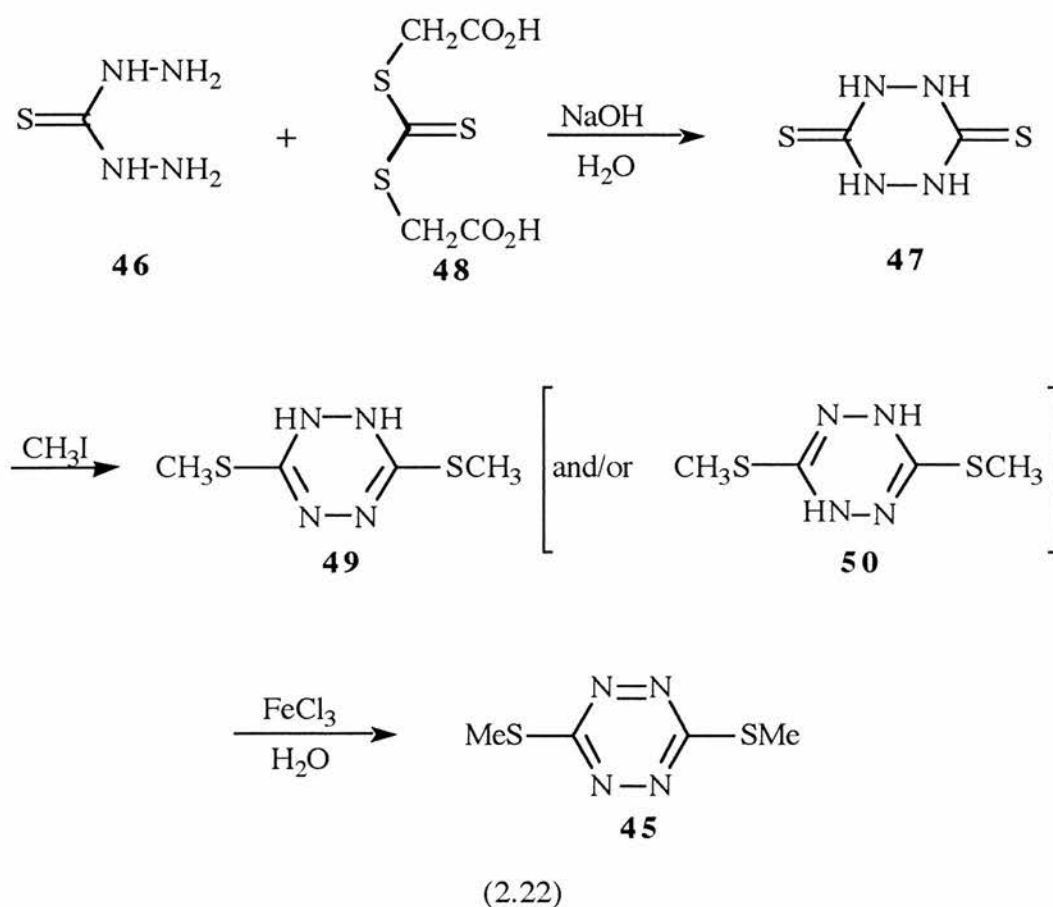
The synthesis of compound **45**[92] is shown in Figure 2.22. Thiocarbohydrazide, **46**, prepared from carbon disulphide and hydrazine, is converted into the tetrahydrotetrazinedithione **47** by reaction with thiocarbodiglycolic acid, **48**. [According to Seitz and his colleagues, this step is a temperamental reaction which either works well or fails altogether, for no obvious reason; however, the author had no

problems in this respect.] The dithione is then methylated on both sulphur atoms, and the resulting bis-(methylthio)dihydrotetrazine (**49** or **50** or a mixture of the two) is oxidised to the fully aromatic tetrazine **45** by aqueous ferric chloride.

As a model reaction, the tetrazine **45** and bis-(p-ethynylphenyl) ether, **36**, were heated together in o-dichlorobenzene at 165°C for 24h, the mixture being analysed by t.l.c. at 2-hourly intervals. At the end of the 24h period the two principal components of the reaction mixture were the unchanged starting materials; only a very small amount of reaction had evidently taken place.

[Subsequent attempts by a colleague to react the more electron-deficient dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with similar diethynyl compounds have also met with only limited success.]

Replacement of one of the methylthio groups in compound **45** by reaction with hydrazine hydrate gave the hydrazinotetrazine **51**[93]; similarly reaction with ammonia and amines gave the aminotetrazines **52**. The nitrogen-containing substituents are susceptible to further reactions which may lead to useful bis-tetrazine monomers. For example, the hydrazino compound **51** may be converted, using iron (III) salts and hydrobromic acid, into the bromotetrazine **53** which readily undergoes nucleophilic displacement reactions with, for example, alcohols[94(a)]. The bis-(methylthio)-tetrazine **45** may undergo displacement reactions with diamines to yield possible bis-tetrazine monomers[94(b)]. The aminotetrazine **52** (R=H) may be expected to undergo acylation at the exocyclic nitrogen, giving **54**. All of these processes (Figure 2.23) can in principle be adapted (e.g. by the use of a diol or a bis-acid chloride) in order to lead to potentially useful bis-(1,2,4,5-tetrazines).

The work described in this chapter has met with varying degrees of success. The original intention was to carry out a broad range of reactions which could be applied to the synthesis of polymers. For many of these reactions which are perfectly applicable in "small-molecule" chemistry, the results have been either entirely negative

or very disappointing. However, some positive results have been obtained and are currently being explored by the research group as a whole.
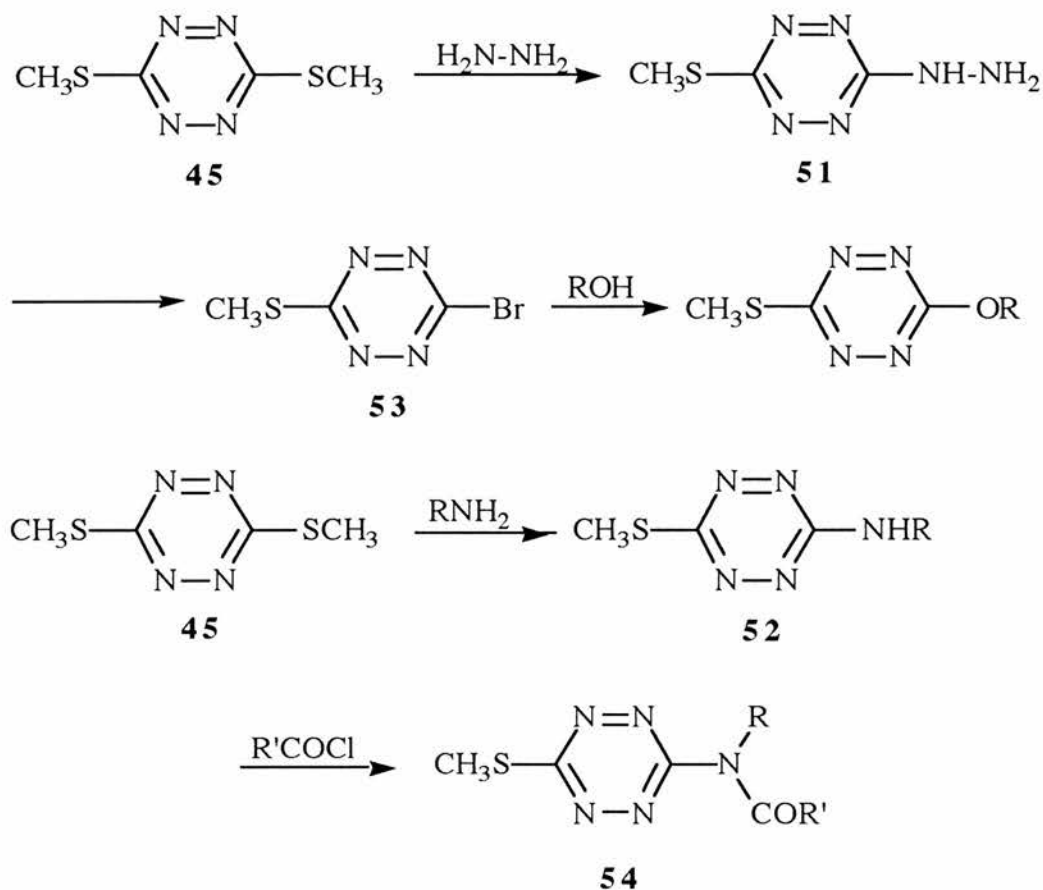
(2.23)

The utilisation of the oxidation of acetyl compounds to their glyoxal counterparts (pp. 38-39) is now leading to a wide variety of novel bis-(1,2,4-triazines) which are being investigated as potential monomers. Their intermolecular reactions with bis-alkynes did not occur as hoped, but appeared to require extremely severe conditions, to the extent that they are unlikely to be of commercial interest. Also, the reaction of a more electron-deficient system (1,2,4,5-tetrazine) with bis-alkynes was similarly discouraging. The two lines being tackled now are:-

(1) Increasing the electron-deficient character of the diene, for example by oxidation of the S-methyl substituent to sulphoxide or sulphone.

(2) Increasing the electron-rich character of the dienophile. The reaction of 1,2,4,5-tetrazines with α-(trimethylsilyloxy)styrene, $CH_2=C(OSiMe_3)Ph$, which is the trimethylsilyl enol ether of acetophenone, proceeds well under relatively mild conditions, and attempts are now being made to expand the scope of this reaction to cover bis-(trimethylsilyl enol ethers). Bis-enamines are also possible synthetic targets, but again these are elusive compounds to produce and purify.

Although the intermolecular reactions of the triazines did not proceed as planned, the same may not be true of the corresponding intramolecular reactions (cf. pp. 26-28), because of the added entropic assistance to reaction. Efforts are still in progress to synthesise bis-phenols containing appropriately positioned alkynyl or other dienophilic groups for further reaction with suitably functionalised bis-triazines (Figure 2.18; p. 46).

Experimental

Materials and apparatus

Melting points were determined on an Electrothermal model 9100 apparatus and are uncorrected.

The infra-red spectra were recorded as Nujol mulls.

Unless otherwise indicated, n.m.r. spectra were recorded in $CDCl_3$ solution, ^1H n.m.r. spectra at 200 MHz and ^{13}C n.m.r. spectra at 50.3 MHz, on a Varian Gemini spectrometer with tetramethylsilane as an internal reference.

Mass spectra were generated on a Finnegan Mat. Incos 50 mass spectrometer.

Symbols and abbreviations

n.m.r.	nuclear magnetic resonance
δ	chemical shift (ppm)
s	singlet
br	broad singlet
d	doublet
dd	double doublet
m	multiplet
i.r.	infra-red
m.p.	melting point
dec.	decomposition

Formation of bis-(*p*-acetylphenyl)ether (**1**)

A solution of diphenyl ether (11.3g, 0.067 mol) in dichloromethane (25 ml) was added dropwise to a stirred suspension of anhydrous aluminium chloride (26.7g, 0.20 mol) in dichloromethane (25 ml), and the mixture was stirred at 0°C for 4h, and then left stirring overnight at room temperature. The resulting solution was then poured into ice-water (300 ml) to quench any aluminium complexes formed. The organic layer was separated and the aqueous layer extracted with dichloromethane (100 ml). The combined organic layers were washed with water, dried over magnesium sulphate, and the solvent was then evaporated, leaving a white solid which was recrystallised from ethanol.

Yield 14.7g (86%), m.p. 99-101°C (lit.[95], 100-101°C).

δ_H 2.60 (6H, s, 2 x CH$_3$), 7.15 and 8.05 (2 x 4H, AA'BB', Ar-H).

Formation of 4,4'-diacetylbiphenyl (**2**).

A solution of biphenyl (10.3g, 0.068 mol) in dichloromethane (25 ml) was added dropwise (at 0°C) to a stirred suspension of anhydrous aluminium chloride (15.7g, 0.20 mol) in dichloromethane (25 ml). The mixture was stirred at 0°C for 4h then at room temperature overnight. The solution formed was then poured slowly (to avoid bumping of the liquid) into ice-water (300 ml), and the mixture stirred for 1h. The white precipitate formed was filtered off and the organic layer separated. The aqueous layer was extracted with dichloromethane, the organic layers were combined and washed with water, dried over magnesium sulphate and the solvent evaporated. The residual solid and the initial precipitate were combined and recrystallised from ethanol.

Yield 13.25g (83%), m.p. 188-190°C (lit.,[96] 189°C).

δ_H 2.65 (6H, s, 2 x CH$_3$), 7.70 and 8.15 (2 x 4H, AA'BB', Ar-H).

Formation of bis-[*p*-(bromoacetyl)phenyl] ether (**4**).

(a) Bromine (4.0g, 0.025 mol) in acetic acid (15 ml) was added dropwise to a solution of bis-(*p*-acetylphenyl) ether (**1**) (3.2g, 0.0125 mol) in acetic acid (40 ml) at

50°C. When addition was completed, the mixture was left stirring overnight at room temperature and the solid formed was filtered off and recrystallised from ethanol.

Yield 2.4g (46%), m.p. 112-116°C (lit.[76], 124°C).

(b) A solution of bromine (4.0g, 0.025 mol) in dichloromethane (15 ml) was added dropwise to a solution of bis-(p-acetylphenyl) ether (3.2g, 0.0125 mol) in dichloromethane (40 ml) heated to 30°C. The mixture was left stirring overnight at room temperature, the solvent was distilled off and the residue was recrystallised from ethanol.

Yield 4.0g (77%), m.p. 113-117°C (lit.[76], 124°C).

δ_H 4.45 (4H, s, CH_2), 7.13 and 8.05 (2 x 4H, AA'BB', Ar-H).

Formation of 4,4'-bis-(p-bromoacetyl)biphenyl (5)

Bromine (4.0g, 0.025 mol) in acetic acid (15 ml) was added dropwise to a warm (*ca*. 50°C) solution of 4,4'-diacetylbiphenyl (2) (3.0g, 0.0125 mol) in acetic acid (40 ml). Upon complete addition the mixture was left stirring overnight at room temperature and the product was filtered off and recrystallised from chloroform.

Yield 2.4g (48%), m.p. 212-213°C (lit.[97] 220-222°C).

δ_H 4.5 (4H, s, 2 x CH_2), 7.60 and 8.10 (2 x 4H, AA'BB', Ar-H).

Formation of 1,4-bis(bromoacetyl)benzene (6).

Bromine (4.0g, 0.025 mol) in acetic acid (15 ml) was added dropwise to a warm solution (*ca*. 40°C) of 1,4-diacetylbenzene (3) (2.0g, 0.0125 mol) in acetic acid (40 ml). After *ca*. 4h at room temperature, the product crystallised; it was filtered off, sucked dry and washed with ethanol. The white product was then recrystallised from ethanol.

Yield 2.40g (60%), m.p. 168°C (lit.[76], 172-173°C)

δ_H 4.45 (4H, s, 2 x CH_2), 8.10 (4H, s, Ar-H).

Attempted oxidation of bis(bromoacetyl) compounds using DMSO.[76]

Solutions of the bis(bromoacetyl) compounds (0.0125 mol) in dimethyl sulphoxide (15 ml) were left at room temperature for 24h. The reaction mixture was

then poured into ice-water and stirred for 1h, and the precipitate which was supposed to form[76] did not; thus the reaction was tried again using various amounts of dimethyl sulphoxide (20-100 ml) and different temperatures (room temperature up to 80°C) and also extraction of the aqueous solution with various solvents (ether, dichloromethane, chloroform) but the reaction did not appear to work, as the proton resonances of the compounds obtained corresponded to the starting material.

Oxidation of the bis-(bromoacetyl) compounds using dimethyl sulphoxide and hydrobromic acid.

48% (8.8M) Hydrobromic acid (17 ml) was slowly added to a stirred solution of the bis-(bromoacetyl) compound (0.025 mol) in dimethyl sulphoxide (85 ml). The solution was stirred at 55°C, and the reaction was monitored by thin-layer chromatography. When the starting material was consumed, the solution was poured on to ice and the solid product was filtered off and dried. Upon characterisation by melting point, however, the values found did not approach the literature values (>30°C difference). The experiments were repeated, but the discrepancies remained.

Conversion of trimethylamine-*N*-oxide dihydrate into anhydrous trimethyl-amine-*N*-oxide

A solution of trimethylamine oxide hydrate (22.2g, 0.2 mol) was dissolved in warm dimethylformamide (140 ml) and then placed in a 250ml 3-necked flask set-up for distillation. The flask was then heated, using an oil-bath, and solvent was distilled off until the boiling point reached 152-153°C. The temperature was reduced along with the pressure (using a water pump) and the rest of the solvent was distilled off. At the end of the distillation the temperature of the bath was slowly raised to *ca.* 120°C. The residual anhydrous trimethylamine-*N*-oxide (14.8g) was dissolved in chloroform (50 ml) and the flask was then sealed. Portions of the anhydrous amine oxide could then be removed from the flask when needed.

Attempted oxidation of bis-(bromoacetyl) compounds using trimethylamine *N*-oxide.

To a solution of anhydrous trimethylamine *N*-oxide (3.75g, 0.05 mol) in chloroform (25 ml), the bis-(bromoacetyl) compound (0.025 mol) was added and the mixture was stirred for 1h. The yellow precipitate was filtered off, treated with dilutre sulphuric acid (1M; 25 ml), then recrystallised from water.

However, the products were not the desired bisglyoxals, as was seen from the melting points (>100°C too high), t.l.c. and ^{1}H n.m.r. spectra, which showed peaks at δ 12, indicating the possible presence of a carboxylic acid. The reaction was attempted several more times, again varying the amount of solvent, temperature (room temperature up to 50°C), and the amount of acid added, but the desired product was not formed, with the product melting points again all at greatly elevated temperatures.

Attempted oxidation of the bis-(bromoacetyl) compounds using pyridine *N*-oxide.

The bis-(bromoacetyl) compound (0.0066 mol) was added to pyridine *N*-oxide (1.25g, 0.013 mol) in acetonitrile (15 ml). The mixture was then stirred for 3h; in this time the solution developed a yellow colour, and a yellow precipitate formed. The whole mixture was treated with aqueous sodium hydroxide (1M; 20 ml), stirred for a further 30 minutes, and the precipitate was then centrifuged out of the mixture and recrystallised from water. Again it was found that the reaction had not worked according to plan. It was discovered in the literature that, when subjected to a strong base, a bis-(ketoaldehyde) can undergo a *benzil-benzilic acid rearrangement* and so the strength of the base was varied but this did not make the reaction work. It was also thought that the precipitate formed originally could be the required product, but from melting point and n.m.r. analysis, this was not the case, with results similar to the trimethylamine *N*-oxide findings, that is, a peak at δ 12 in the ^{1}H nmr. Again the reaction was repeated, varying the solvent (chloroform, water, dichloromethane), reaction temperature (room temperature up to 80°C), reaction duration (20 minutes up

to 3h), and the amounts of sodium hydroxide and pyridine *N*-oxide added, but none of these led to any significant improvement of the results.

Oxidation of the diacetyl compounds using selenium dioxide.

Selenium dioxide (7.4g, 0.067 mol) in dioxan (35 ml) and water (1.3 ml) containing concentrated hydrochloric acid (2 drops) was heated to 60°C. The diacetyl compound (0.034 mol) was then added and the mixture was refluxed for 4h, during which time selenium precipitated out. The solution was then filtered (hot) and the filtrate cooled to give a dark red liquid, which was then refiltered to remove any remaining selenium.

The liquid was then concentrated under reduced pressure and the remaining solid was recrystallised from dioxan:water (1:2). The melting points (>40°C different from the literature) and appearances of the products (brown and dark red solids) bore no relation to those described in the literature[76]; repetition of the reactions gave similar results.

Variation of the solvent (acetic anhydride)[72(a)], the amounts of water, dioxan, and acid, the reaction temperature (80-120°C) and reaction duration (4-8h) gave products which still did not meet the literature standards.

Formation of phenylglyoxal hydrate (**13**)

48% (8.8M) Hydrobromic acid (17 ml, 0.15 mol) was added dropwise to a solution of acetophenone (**7**) (6.0g, 0.05 mol) in dimethyl sulphoxide (85 ml), and the resulting solution was heated to 55°C and stirred for 6h, then poured into ice/water(400 ml). A white precipitate was formed, which was filtered off, washed with water, and then recrystallised form water, giving a white, crystallline product.

Yield 6.4g (84%), m.p. 89-90.5°C (lit.[98], 91°C).

Formation of *p*-nitrophenylglyoxal hydrate (**14**)

(a) Selenium dioxide (3.0g, 0.027 mol) was added to a mixture of dioxan (15 ml), water (2.5 ml) and a few drops of conc. HCl. The mixture was then heated to 60°C, *p*-nitroacetophenone (**8**) (4.46g, 0.027 mol) in dioxan (10 ml) was then added,

and the resulting mixture was heated under reflux for 10h. After this time, the mixture was filtered hot (to remove black selenium precipitated during the reaction). The resulting red filtrate was left to cool down and then refiltered to remove further red selenium. This filtration was done several times to minimise the amount of selenium impurity present. The final filtrate was then concentrated under reduced pressure, leaving a yellow/brown paste (1.91g, 36%) which was then taken through, without purification, to the next stage.

(b) 48% (8.8M) Hydrobromic acid (17 ml, 0.15 mol) was added dropwise to a solution of *p*-nitroacetophenone (**8**) (8.25g, 0.05 mol) in dimethyl sulphoxide (85 ml), and the resulting solution was heated to 55°C and stirred for 6h, with an accompanying colour change from clear to orange-red. The reaction mixture was then poured into ice/water (400 ml); initially the mixture turned cloudy but upon cooling, no precipitate was observed. It was then decided to take the mixture directly through to the next stage.

Formation of *p*-bromophenylglyoxal hydrate (**15**)

(a) Selenium dioxide (3.0g, 0.027 mol) was added to a mixture of dioxan (15ml) and water (2.5 ml) containing three drops of conc. HCl, and the mixture was then heated to 60°C. *p*-Bromoacetophenone (**9**) (5.38g, 0.027 mol) in dioxan (10 ml) was then added and the resulting mixture was heated under reflux for 10h.. After this time, the mixture was filtered hot (to remove the black selenium precipitated during the reaction). The resulting red coloured material was then left to cool down and then filtered again to remove further red selenium. The remaining solution was then concentrated under reduced pressure, leaving behind an off-white paste, which was then boiled up in water, treated with charcoal, and filtered hot. Upon cooling, the product was filtered and dried giving white, needle-like crystals.

Yield 2.7 g (43%), m.p. 109-112.5°C [lit.[99(a)] 51-52°C (anhydrous), [99(a)] 132°C, [99(b)] 125°C - hydrated]

δ_H (CDCl$_3$/d$_6$-DMSO) 5.79 (2H, s, OH), 6.15 [1H, s, C$\underline{H}$(OH)$_2$], 7.62 and 8.01 (4H, AA'BB', Ar-H)

(b) 48% (8.8M) Hydrobromic acid (17 ml, 0.15 mol) was added dropwise to a solution of *p*-bromoacetophenone (**9**) (9.95g, 0.05 mol) in dimethyl sulphoxide (85 ml), and the resulting solution was heated to 55°C and stirred for 6h, with an accompanying colour change from clear to yellow-green. The reaction mixture was then poured into ice/water (400 ml) and a white precipitate was formed, which was then filtered off, washed with water, and recrystallised from water, leaving a white, crystalline product.

Yield 10.1 g (87%), m.p. 111-113.5°C

Formation of *p*-hydroxyphenylglyoxal hydrate (**16**)

(a) Selenium dioxide (5.56g, 0.05 mol) was added to a solution of dioxan (30 ml), water (5 ml) and a few drops of conc. HCl, and the mixture was then heated to 60°C. *p*-Hydroxyacetophenone (**10**) (6.8g, 0.027 mol) in dioxan (20 ml) was then added, and the resulting mixture was heated under reflux for 10h. The mixture was then filtered hot (to remove black selenium precipitated during the reaction), the resulting orange-coloured filtrate was left to cool down and then refiltered to remove further red selenium. This filtration was done several times to minimise the amount of selenium impurity present. The resultant solution was then concentrated under reduced pressure, leaving a brown crusty paste, which was then boiled up in water, treated with charcoal, and fitered hot. Upon cooling, the product was filtered off and dried, leaving an off-white, crystalline solid.

Yield 3.14g (37%), m.p.70-72°C [lit.[100(a)] 88-90°C (anhydrous), [100(b)] 111-112°C (hydrated)]

δ_H (d$_6$-DMSO) 5.60 [3H, s, CH(OH)$_2$, signals coincident], 8.25 (4H, s, Ar-H).

(b) 48% (8.8M) Hydrobromic acid (17 ml, 0.15 mol) was added dropwise to a solution of *p*-hydroxyacetophenone (**10**) (6.8g, 0.05 mol) in dimethyl sulphoxide (85 ml), and the resulting solution was heated to 55°C and stirred for 6h, with an accompanying colour change from clear to green. The reaction mixture was then poured

into ice/water (400 ml) and left to cool, but no precipitate formation was observed, as had been with previous glyoxals. The mixture was extracted with ether three times and the ether extracts were combined, dried over magnesium sulphate, and concentrated under reduced pressure. The resultant brown oil was left in a refrigerator overnight. In the morning a white solid had been formed: this was dissolved in boiling water, and the solution was filtered hot and left to recrystallise. The product was then collected and dried to yield a white crystalline material.

Yield 3.6g (42%), m.p. 71-73°C

Formation of p-acetamidoacetophenone

Solid p-aminoacetophenone (12) (27.0g, 0.2 mol) was added gradually to a stirred mixture of acetic anhydride (180 ml) and pyridine (20 ml). The solid dissolved, heat was evolved and a white product precipitated after several minutes. After 5h at room temperature, the product was filtered off, washed with water, and recrystallised from propan-2-ol.

Yield 24.8g (70%), m.p. 168-169°C (lit.[101], 171°C).

δ_H 2.10 (3H, s, CH_3COAr), 2.45 (3H, s, CH_3CON), 3.42 (1H, s, NH), 7.68 and 7.84 (2 x 2H, AA'BB', Ar-H)

Formation of p-acetamidophenylglyoxal hydrate (17)

Selenium dioxide (3.0g, 0.027 mol) was added to a mixture of dioxan (15 ml), water (2.5 ml), and a few drops of conc. HCl. The mixture was then heated to 60°C. p-Acetamidoacetophenone (4.78g, 0.027 mol) in dioxan (10 ml) was then added, and the resulting mixture was heated under reflux for 10h, then filtered hot (to remove black selenium precipitated during the reaction). The resulting yellow-orange solution was left to cool down and then refiltered to remove further red selenium. The resulting pale yellow filtrate was then concentrated under reduced pressure, leaving an off-white solid. This solid was dissolved in boiling water, and the solution treated with charcoal. Upon cooling, a whitish solid crystallised out.

Yield 2.01g (36%), m.p. 110-114°C (lit.[102], 133-135°C - hydrated)

δ_H (d_6-DMSO) 2.09 (3H, s, CH$_3$), 5.68 [1H, br, C$\underline{H}$(OH)$_2$], 6.64 (2H, d, *J ca.* 7 Hz, OH), 7.71 and 8.04 (4H, AA'BB', Ar-H), and 10.28 (1H, s, NH)

Formation of *p,p'*-oxybis(phenylglyoxal) (**19**)

48% (8.8M) Hydrobromic acid (17 ml, 0.15 mol) was added dropwise with stirring over 20 min. to a solution of bis-(*p*-acetylphenyl) ether (**1**) (6.35g, 0.025 mol) in dimethyl sulphoxide (80 ml). The temperature was raised to 60°C and stirring continued at this temperature for 24h. The yellow solution was allowed to cool and was then poured into ice-water (400 ml).

The white solid obtained was filtered off, washed with water (200 ml) and sucked dry. The bis-glyoxal was then recrystallised from dioxan-water (1:1).

Yield 3.1g (39%), m.p. 139-142°C (dec.) (lit.[72(b)], 122°C; [76] 124-127°C; [103] 140.5-142°C)

i.r. v_{max} (C=O) 1685 cm^{-1}

δ_H (d_6-DMSO) 5.67 [2H, s, C$\underline{H}$(OH)$_2$], 6.18 (4H, br s, OH), 7.12 and 8.15 (8H, AA'BB', Ar-H).

Formation of 4,4'-diglyoxalylbiphenyl (**20**)

48% (8.8M) Hydrobromic acid (17 ml, 0.15 mol) was added dropwise with stirring over 20 min. to a solution of 4,4'-diacetylbiphenyl (**2**) (5.95g, 0.025 mol) in dimethyl sulphoxide (80 ml). The temperature was raised to 60°C and stirring continued at this temperature for 24 h. The yellow/green solution was allowed to cool and was then poured into ice-water (400 ml).

The white solid obtained was filtered off, washed with water (200 ml) and sucked dry. The bis-glyoxal was then recrystallised from dioxan-water (1:1).

Yield 4.23g (56%), m.p. 116-118°C (dec.) (lit.[97], 130-145°C; [76] 150°C)

i.r. v_{max} (C=O) 1685 cm^{-1}

δ_H (d_6-DMSO) 5.74 [2H, s, 2 x C$\underline{H}$(OH)$_2$], 6.84 (4H, s, OH), 7.92 and 8.20 (8H, AA'BB', Ar-H).

Formation of *p*-phenylenebisglyoxal (**21**)

48% (8.8M) Hydrobromic acid (17 ml, 0.15 mol) was added dropwise with stirring over 20 min. to a solution of 1,4-diacetylbenzene (**3**) (4.05g, 0.025 mol) in dimethyl sulphoxide (80 ml). The temperature was raised to 60°C and stirring continued at this temperature for 24h. The yellow solution was allowed to cool and was then poured into ice-water.

The product did not precipitate so the aqueous mixture was extracted with ethyl acetate (3 x 200 ml), and the extract washed with aqueous sodium hypochlorite solution (10%, 300 ml), then with water, dried over magnesium sulphate, and concentrated *in vacuo*. The bis-glyoxal was then recrystallised from dioxan-water (1:1).

Yield 0.85g (15%), m.p. 152-154°C (dec.) (lit.[72(a)], 110-111°C; [76], 144-147°C; [97], 138-158°C)

i.r. ν_{max} (C=O) 1685 cm^{-1}

δ_H (d$_6$-DMSO) 3.74 (4H, br, OH), 5.65 [2H, s, C$\underline{H}$(OH)$_2$], 8.22 (4H, s, Ar-H)

Formation of bis-[(*p*-phenylacetyl)phenyl] ether (**22**)

A solution of phenylacetyl chloride (30.9g, 0.2 mol) in dichloromethane (50 ml) was added dropwise to a suspension of diphenyl ether (17.0g, 0.1mol) and anhydrous aluminium chloride (26.6g, 0.2 mol) in dichloromethane (200 ml) at ambient temperature. The resulting brown mixture was stirred at room temperature (with the exclusion of air) for 24h and then poured into a mixture of ice/conc. HCl (600 ml). The organic phase was separated and washed with water, aqueous sodium hydrogen carbonate, then water, followed by drying over magnesium sulphate. The solution was concentrated to about 60 ml and then was cooled, giving rise to a cream-coloured solid. The solid was recrystallised from toluene, giving an off-white solid.

Yield 28.9g (71%), m.p. 168-169°C (lit.[80], 169-170°C)

δ_H 4.35 (4H, s, 2 x CH$_2$), 7.05 and 7.95 (8H, AA'BB', Ar-H), 7.2-7.4 (10H, m, Ph-H).

Formation of bis-[p-(α-bromo-α-phenylacetyl)phenyl] ether (**23**)

Bis-[(p-phenylacetyl)phenyl] ether (**22**) (4.06g, 0.01 mol) was dissolved in a minimum amount of chloroform by heating and stirring; the solution was then cooled and bromine (3.2g, 0.02 mol) was added over 2h. Upon complete addition the reddish-brown mixture was refluxed for 4h (to ensure complete HBr evolution) and the product was isolated by removal of the chloroform under reduced pressure. The crude product was then dissolved in ether, extracted with water and then aqueous sodium hydrogen carbonate to remove any inorganics, and the organic layer was evaporated off, giving a resinous product which was then sucked dry on a water-pump, giving a fine powder-like product.

N.B. Care must be taken when sucking dry on the water-pump, as upon removal of residual ether, the product "candy-flosses" out and fills the whole of the flask.

Yield 3.56g (63%), m.p. 87-89°C (lit.[104(a)] m.p. not quoted; [104(b)] 54-56°C).

δ_H (CDCl$_3$/d$_6$-DMSO) 6.35 (2H, s, 2 x CHBr), 7.05 and 8.05 (8H, AA'BB', Ar-H), 7.25-7.70 (10H, m, Ph-H).

Formation of p,p'-oxydibenzil (**24**)
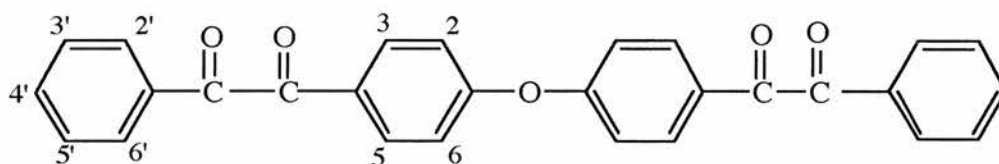
The bis-α-bromoketone (**23**) (11.28g, 0.02 mol) was dissolved in dimethyl sulphoxide (20 ml) and the reaction mixture was heated and stirred at 80°C for 5h. The mixture was cooled and then poured into methanol (100 ml) and the yellow precipitate formed was then collected, washed with methanol, water, sodium hypochlorite solution (to remove any residual dimethyl sulphide), water, methanol and then air-dried in a fume cupboard.

Yield 6.86g (79%), m.p. 103-105°C

δ_H 7.34 and 8.08 (8H, AA'BB', 2,3,5,6-H), 7.67 (4H, t, 3',5'-H), 7.85 (2H, t, 4'-H), 7.96 (4H, t, 2',6'-H).

Formation of *p,p'*-oxydibenzil (24), bypassing the bisbrominated intermediate

Bis-[(*p*-phenylacetyl)phenyl]ether (22) (5.075g, 0.0125 mol) was placed in a 100 ml flask with dimethyl sulphoxide (45 ml) and heated at 55°C. 48% (8.8M) Hydrobromic acid (8.5 ml, 0.075 mol) was added dropwise over 20 minutes and the resulting solution was kept stirring at a constant 55°C for 18h. The solution was then poured into ice/water (400 ml) and the resulting yellow precipitate was then filtered off, washed with methanol, water, sodium hypochlorite solution (to remove any residual dimethyl sulphide) and then water. The product was then recrystallised from methanol.

Yield 2.04g (38%), m.p. 104-107°C (lit.[80], 106.4-107.4°C; [103], 108-109°C)

δ_H 7.36 and 8.07 (8H, AA'BB'), 7.64 (4H, t), 7.83 (2H, t), 7.92 (4H, t) (assignments as above).

S-Methylation of thiosemicarbazide

Thiosemicarbazide (9.1g, 0.1 mol) was heated under reflux with iodomethane (14.2g, 0.1 mol) in absolute ethanol until a sample solidifed on a watchglass in crystalline form. This took approximately 90 minutes. The hot solution was then poured into a beaker and the salt soon crystallised. The salt was then recrystallised from absolute ethanol .

Yield 19.6g (84%), m.p. 134-135°C (lit.[81], 136°C).

Formation of 3-methylthio-5-phenyl-1,2,4-triazine (25)

48% (8.8M) Hydrobromic acid (17 ml, 0.15 mol) was added dropwise to a solution of acetophenone (7) (6.0g, 0.05 mol) in dimethyl sulphoxide (85 ml). The resulting solution was heated to 55°C and stirred for 6h, with an accompanying colour

change from clear to yellow-green. The reaction mixture was then poured into ice/water (600 ml), upon which a white precipitate was formed. After 1h the reaction mixture was stirred and neutralised (pH 7) using sodium hydrogen carbonate (checked by pH paper). Further sodium hydrogen carbonate (4.62g, 0.055 mol, 1.1 mol eq.) was added, then S-methylthiosemicarbazidium iodide (11.65g, 0.05 mol) in water (100 ml) was added dropwise and the reaction mixture was left stirring at room temperature for 24 h. After this time the yellow precipitate which had formed was filtered off, washed with water, dried and then recrystallised from ethanol.

Yield 6.91g (68%), m.p. 94-97°C (lit.[83], 94°C)

δ_H 2.68 (3H, s, CH_3), 7.45-7.6 (3H, m, Ar-H), 8.08 (2H, d, Ar-H), 9.42 (1H, s, 6-H)

δ_C 13.8 (CH_3), 127.5 (C-3'), 129.2 (C-2'), 132.6 (C-4'), 132.8 (C-1'), 141.7 (C-6), 154.2 (C-5), 173.5 (C-3)

<u>Formation of 3-methylthio-5-(p-nitrophenyl)-1,2,4-triazine (**26**)</u>
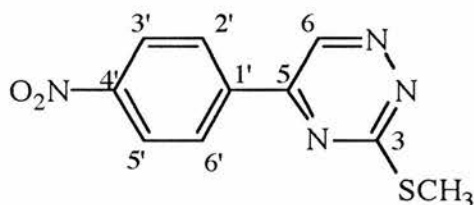
(a) Selenium dioxide (3.0g, 0.027 mol) was added to a mixture of dioxan (15 ml), water (2.5 ml) and a few drops of conc. HCl, and the mixture was then heated to 60°C. p-Nitroacetophenone (**8**) (4.46g, 0.027 mol) in dioxan (10 ml) was then added to the solution and the resulting mixture was heated under reflux for 10h. The mixture was filtered hot (to remove black selenium precipitated during the reaction), the resulting red solution was then left to cool down and then refiltered to remove further red selenium. The resultant yellow filtrate was then diluted with water (300 ml) and sodium hydrogen carbonate (2.5g, 1.1 mol eq.) was added. To this liquid, S-methylthiosemicarbazidium iodide (6.3g, 0.027 mol) in water (100 ml) was added dropwise. The reaction mixture was left at room temperature for 24h and then the dark

yellow precipitate formed was filtered off, washed with water, dried and then recrystallised from acetic acid.

Yield 2.45g (37%), m.p. 224-227°C

(b) 48% (8.8M) Hydrobromic acid (17 ml, 0.15 mol) was added dropwise to a solution of *p*-nitroacetophenone (**8**) (8.25g, 0.05 mol) in dimethyl sulphoxide (85 ml), and the resulting solution was heated to 55°C and stirred for 6h, with an accompanying colour change from clear to orange-red. The reaction mixture was poured into ice/water (600 ml) and left to cool; it was then neutralised (pH 7) using sodium hydrogen carbonate (checked by pH paper) with an accompanying colour change from orange-red to pale yellow. The solution was then treated with further sodium hydrogen carbonate (4.62g, 0.055 mol, 1.1mol eq.) and then *S*-methylthiosemicarbazidium iodide (11.65g, 0.05 mol) in water (100 ml) was added dropwise and the reaction mixture was left stirring at room temperature for 24h. After this time the dark yellow precipitate which had formed was filtered off, washed with water, dried, and recrystallised from acetic acid.

Yield 5.2g (42%), m.p. 226-228°C

Found: C, 48.6; H, 3.05; N, 22.8. $C_{10}H_8N_4O_2S$ requires C, 48.4; H, 3.25; N, 22.6%.

δ_H 2.76 (3H, s, CH_3), 8.35 and 8.41 (4H, AA'BB', 2', 3', 5', 6'-H), 9.45 (6-H)

δ_C (CDCl$_3$/d$_6$-DMSO) 13.3 (CH_3), 124.1 (C-3'), 129.3 (C-2'), 138.8 (C-1'), 143.0 (C-6), 149.8 (C-4'), 152.2 (C-5), and 172.8 (C-3)

Formation of 5-(*p*-bromophenyl)-3-methylthio-1,2,4-triazine (**27**)
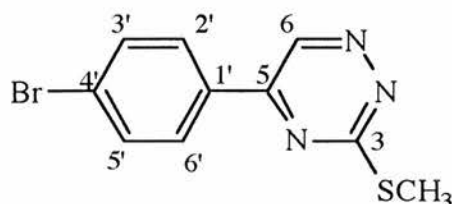
(a) Selenium dioxide (3.0g, 0.027 mol) was added to a mixture of dioxan (15 ml), water (2.5 ml) and a few drops of conc. HCl, and the mixture was then heated to

60°C. *p*-Bromoacetophenone (**9**) (5.38g, 0.027 mol) in dioxan (10 ml) was added, and the resulting mixture was heated under reflux for 10h then filtered hot (to remove the black selenium precipitated during the reaction). The resulting red-coloured solution was then left to cool down and then filtered again to remove further red selenium. The resultant yellow filtrate was then diluted with water (300 ml), sodium hydrogen carbonate (2.5g, 1.1 mol eq.) was added, and *S*-methylthiosemicarbazidium iodide (6.3g, 0.027 mol) in water (100 ml) was then added dropwise. The reaction was left at room temperature for 24h and then the pale yellow precipitate formed was filtered off, washed with water, dried and recrystallised from ethanol, yielding fine, needle-like crystals.

Yield 2.77g (36%), m.p. 154-157°C

(b) 48% (8.8M) Hydrobromic acid (17 ml, 0.15 mol) was added dropwise to a solution of *p*-bromoacetophenone (**9**) (9.95g, 0.05 mol) in dimethyl sulphoxide (85 ml). The resulting solution was heated to 55°C and stirred for 6h, with an accompanying colour change from clear to yellow-green. The reaction mixture was then poured into ice/water (600 ml), upon which a white precipitate was formed. After 1h the reaction mixture was stirred and neutralised (pH 7) using sodium hydrogen carbonate (checked by pH paper). Further sodium hydrogen carbonate (4.62g, 0.055 mol, 1.1 mol eq.) was added, then *S*-methylthiosemicarbazidium iodide (11.65g, 0.05 mol) in water (100 ml) was added dropwise and the reaction mixture was left stirring at room temperature for 24 h. After this time the yellow precipitate which had formed was filtered off, washed with water, dried and then recrystallised from ethanol.

Yield 10.3g (73%), m.p. 156-159°C

Found: C, 42.6; H, 2.7; N, 14.9. $C_{10}H_8BrN_3S$ requires C, 42.6; H, 2.9; N, 14.9%.

δ_H 2.72 (3H, s, CH_3), 7.68 and 8.04 (4H, AA'BB', Ar-H), 9.45 (1H, s, 6-H)

δ_C 13.9 (CH_3), 127.7 (C-4'), 129.0 (C-2'), 132.0 (C-1'), 132.7 (C-3'), 141.5 (C-6), 153.5 (C-5), and 173.8 (C-3)

m/z 281/283 (M^{+}·) (31%), 181/183 (12), 180/182 (100), 102 (13), 101 (57), 76 (12), 75 (42), 74 (15), 51 (24), 50 (18), etc.

Formation of 5-(*p*-hydroxyphenyl)-3-methylthio-1,2,4-triazine (**28**)
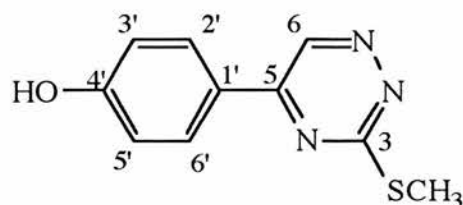
(a) Selenium dioxide (3.0g, 0.027 mol) was added to a mixture of dioxan (15 ml), water (2.5 ml) and a few drops of conc. HCl, and the mixture was heated to 60°C. *p*-Hydroxyacetophenone (**10**) (3.68g, 0.027 mol) in dioxan (10 ml) was then added to the solution and the resulting mixture was heated under reflux for 10h. The mixture was then filtered hot (to remove black selenium precipitated during the reaction),. the resulting orange filtrate was left to cool down and then refiltered to remove further red selenium. The orange filtrate was then diluted with water (300 ml), sodium hydrogen carbonate (2.5g, 1.1 mol eq.) was added, and *S*-methylthiosemicarbazidium iodide (6.3g, 0.027 mol) in water (100 ml) was added dropwise. The reaction was left at room temperature for 24h, and the pale yellow precipitate formed was filtered off, washed with water, dried and recrystallised from ethanol.

Yield 1.77g (28%), m.p. 232-235°C

(b) 48% (8.8M) Hydrobromic acid (17 ml, 0.15 mol) was added dropwise to a solution of *p*-hydroxyacetophenone (**10**) (6.8g, 0.05 mol) in dimethyl sulphoxide (85 ml). The resulting solution was heated to 55°C and stirred for 6h, with an accompanying colour change from clear to green. The reaction mixture was then poured into ice/water (600 ml) and left to cool. After cooling the reaction mixture was stirred and neutralised (pH 7) using sodium hydrogen carbonate (checked by pH paper).

Further sodium hydrogen carbonate (4.62g, 0.055 mol, 1.1 mol eq.) and then *S*-methylthiosemicarbazidium iodide (11.65g, 0.05 mol) in water (100 ml) was added dropwise and the reaction mixture was left stirring at room temperature for 24h. The

yellow precipitate which had formed was filtered off, washed with water, dried and then recrystallised from ethanol.

Yield 5.21g (48%), m.p. 239-240°C

Found: C, 54.4 ; H, 4.1; N, 18.8. $C_{10}H_9N_3OS$ requires C, 54.8; H, 4.1; N, 19.2%.

δ_H (CDCl$_3$/d$_6$-DMSO) 2.69 (3H, s, CH$_3$), 7.02 and 8.18 (4H, AA'BB', Ar-H), 8.32 (1H, s, OH), 9.60 (1H, s, 6-H)

δ_C (d$_6$-DMSO) 13.4 (CH$_3$), 116.5 (C-3'), 124.0 (C-1'), 130.3 (C-2'), 142.2 (C-6), 154.0 (C-5), 162.5 (C-4'), 172.2 (C-3)

m/z 219 (M$^{+\cdot}$) (34%), 119 (13), 118 (100), 89 (12), 64 (8), 63 (11), 55 (7), etc.

Formation of 5-(*p*-acetamidophenyl)-3-methylthio-1,2,4-triazine (**29**)
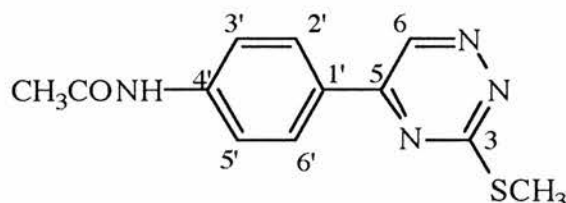
Selenium dioxide (3.0g, 0.027 mol) was added to a mixture of *p*-acetamidoacetophenone (4.78g, 0.027 mol), dioxan (25 ml) and water (5 ml). The mixture was heated and stirred under reflux for 8h. The black selenium formed was then filtered off and the orange filtrate was left to cool overnight. The red selenium was then filtered off, the yellow filtrate was diluted with water (400 ml) and sodium hydrogen carbonate (2.5g, 1.1 mol eq.) was added.

To this liquid, *S*-methylthiosemicarbazidium iodide (6.3g, 0.027 mol) in water (100 ml) was added dropwise. The reaction was left at room temperature for 16 h and then the yellow precipitate formed was filtered off, washed with water, dried and then recrystallised from ethanol:acetic acid (10:1).

Yield 2.31g (33%), m.p. 239-240°C

Found: C, 55.0; H, 4.6; N, 21.2. $C_{12}H_{12}N_4OS$ requires C, 55.4; H, 4.65; N, 21.5%.

δ_H (d$_6$-DMSO) 2.12 (3H, s, CH$_3$CO), 2.67 (3H, s, CH$_3$S), 7.80 and 8.28 (4H, AA'BB', 2',3',5',6'-H), 9.73 (1H, s, 6-H), and 10.34 (1H, s, NH)

δ_C (d$_6$-DMSO) 13.4 (CH$_3$S), 24.5 ($\underline{C}$H$_3$CO), 119.2 (C-3'), 126.9 (C-1'), 129.1 (C-2'), 142.5 (C-4'), 143.9 (C-6), 153.7 (C-5), 169.3 (CO), 172.2 (C-3)

m/z 260 (M^{+}·) (29%), 201 (12), 185 (11), 183 (11), 159 (25), 129 (14), 118 (14), 117 (79), 97 (14), 90 (18), 83 (29), 77 (30), 73 (34), 69 (36), etc. (base peaks at 43 and 45)

"One-pot" oxidation of the diacetyl compounds and subsequent reaction with S-methylthiosemicarbazide.

The oxidation of the diacetyl compounds was done as previously stated, but after the second filtration, water (200 ml) was added to the liquid, which changed the colour from dark red to pale yellow . The mixture was cooled in an ice-bath and the theoretical amount of sodium hydrogen carbonate was added. The theoretical amount of S-methylthiosemicarbazidium iodide was then dissolved in water and then added to the cooled solution, which was then left stirring at 0°C for 4h. A yellow/orange precipitate was formed, which was filtered off, suspended in ethanol to remove any impurities, then analysed by ¹H n.m.r., the results of which were promising, that is there was a small amount of triazine formed, but there were several products present, seen from t.l.c. analysis, and recrystallisation from ethanol still gave a mixture of products.

Formation of bis-[p-(3-methylthio-1,2,4-triazin-5-yl)phenyl] ether (**30**)
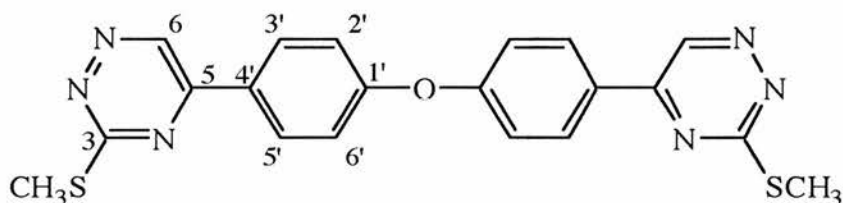
S-Methylthiosemicarbazidium iodide (2.33g, 0.01 mol) in aqueous ethanol (30 ml) was added to a solution of the bis-glyoxal (**19**) (1.59g, 0.005 mol) and sodium hydrogen carbonate (0.93g, 0.011 mol) in aqueous ethanol (50 ml). The resulting yellow mixture was then left stirring at room temperature for 2 days. The mixture was

then extracted with dichloromethane (4 x 75 ml) and the extracts were then combined and washed with water (200 ml) and then dried over magnesium sulphate. The solvent was then removed *in vacuo* and an orange foam was produced. The product was then recystallised from ethanol.

Yield 0.51g (24%), m.p. 184-187°C

Found: C, 57.1; H, 3.6; N, 20.0. $C_{20}H_{16}N_6OS_2$ requires C, 57.1; H, 3.8; N, 20.0%.

(analytical sample prepared by Miss G.A. McLean.)

δ_H 2.74 (6H, s, 2 x CH_3), 7.20 and 8.20 (8H, AA'BB', 2',3',5',6'-H), 9.36 (2H, s, 2 x 6-H)

δ_C (d_6-DMSO) 13.9 (CH_3), 119.8 (C-2' and 6'), 128.8 (C-3' and 5'), 129.9 (C-4'), 141.6 (C-6), 153.6 (C-5), 173.7 (C-3).

Formation of *p,p'*-bis-(3-methylthio-1,2,4-triazin-5-yl)biphenyl (**31**)
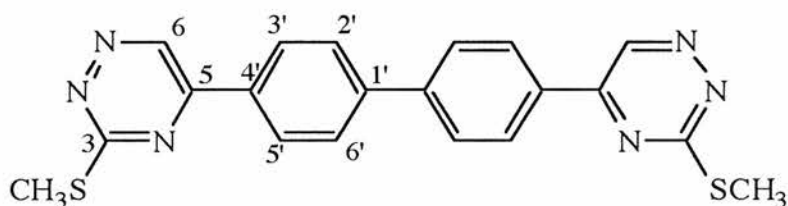
(with G.A. McLean)

S-Methylthiosemicarbazidium iodide (2.33g, 0.01 mol) in aqueous ethanol (30 ml) was added to a solution of the bis-glyoxal (**20**) (1.51g, 0.005 mol) and sodium hydrogen carbonate (0.93g, 0.011 mol) in aqueous ethanol (50 ml). The resulting yellow mixture was then left stirring at room temperature for 2 days. The mixture was then extracted with dichloromethane (4 x 75 ml) and the extracts were then combined and washed with water (200ml) and then dried over magnesium sulphate. The solvent was then removed *in vacuo* and an orange foam was produced. The product was then recystallised from ethanol.

Yield 0.42g (21%), m.p. 243-245°C

Found: C, 59.25; H, 3.9; N, 20.6. $C_{20}H_{16}N_6S_2$ requires C, 59.4; H, 4.0; N, 20.8%

δ_H (d_6-DMSO) 2.74 (6H, s, 2 x CH_3), 7.85 and 8.28 (8H, AA'BB', 2',3',5',6'-H), and 9.41 (2H, s, 2 x 6-H)

δ_C 14.0 (CH_3), 126.9 (C-2' and 6'), 128.0 (C-3' and 5'), 133.0 (C-4'), 141.8 (C-6), 143.8 (C-1'), 153.9 (C-5), and 173.9 (C-3)

Attempted formation of the bistriazines, bypassing the tetracarbonyl compounds.[84]

The bisbrominated compounds (0.0345 mol) and S-methylthiosemicarbazide (0.069 mol) in ethanol (100 ml) were heated at 70-75°C for 3h, and then the ethanol was evaporated. Attempts to take up the black, viscous residue in chloroform proved unsuccessful. Other solvents were tried but the same result was found, that is, an almost complete insolubility. T.l.c. of the small amount that was soluble in acetone showed that there were several components in the material produced. The reaction was then repeated in chloroform but a similar result was obtained.

Attempted formation of terephthaloyl/isophthaloyl linked triazines (32/33)

To a solution of sodium hydroxide (0.4g, 0.01 mol) in dry ethanol (40 ml), 5-(p-hydroxyphenyl)-3-methylthio-1,2,4-triazine (28) (2.19g, 0.01 mol) was added at once. To this a solution of isophthaloyl or terephthaloyl chloride (1.02g, 0.005 mol) in dry ethanol (20 ml) was added at once and the mixture was covered and left stirring at room temperature for 24h. The precipitate formed was filtered off and recrystallised from ethanol. Upon analysis, it was seen that the product obtained was the starting triazine. The reaction was repeated several times, varying the temperature (up to *ca.* 60°C) and the solvent system was varied (dry methanol) but there was only recovery of the starting triazine.

Attempted formation of 5-(*p*-aminophenyl)-3-methylthio-1,2,4-triazine (**34**)

To a solution of sodium hydroxide (0.4g, 0.01 mol) in dry ethanol (30 ml), 5-(*p*-acetamidophenyl)-3-methylthio-1,2,4-triazine (**29**) (2.60g, 0.01 mol) was added at once. The mixture was covered and left stirring at room temperature overnight. The precipitate formed was filtered off and washed with water. Upon analysis, it was seen that the product obtained was the starting triazine. The reaction was repeated several times, varying the temperature (up to reflux) but there was only recovery of the starting triazine.

Formation of bis-(*p*-ethynylphenyl) ether (**36**)

Phosphoryl chloride (18.6 ml, 0.2 mol) was added dropwise, with stirring, over 30 minutes to dry *N,N*-dimethylformamide (100 ml).under an argon atmosphere. The mixture was stirred for another thirty minutes, then bis-(*p*-acetylphenyl) ether (**1**) (12.7g, 0.05 mol) was added at once to the orange/red solution. The mixture was then heated to 60°C and stirred for 5h while still under argon. The solution was cooled to room temperature and poured into ice/water (500 ml), the dark solution formed then being neutralised (pH 7) by gradual addition of solid sodium hydrogen carbonate.

N.B. Care must be taken when adding the sodium hydrogen carbonate, as the mixture effervesces vigorously and rapid addition can result in frothing over of the liquid.

The neutral solution was set aside overnight in a refrigerator. The bis-(β-chlorocinnamaldehyde) formed was then filtered off, washed with water (2 x 150 ml), dissolved in dichloromethane (450 ml), washed with dilute brine (3 x 100 ml) and then dried over magnesium sulphate. The solvent was then removed *in vacuo* to give the cleaned product (8.3g, 48%), which was then taken forward to the next preparative step without any further purification.

A solution of sodium hydroxide (1.92g, 0.048 mol) in dioxan:water (90 ml, 3:2) was heated to 80°C, and the bis-(β-chlorocinnamaldehyde) (4.16g, 0.012 mol) was then added in one portion. The mixture darkened rapidly and was left stirring at

80°C for 30 minutes, cooled to room temperature and then poured into dilute brine solution (250 ml). This solution was then extracted with dichloromethane (1 x 150 ml, then 3 x 75 ml), and the combined extracts were dried over magnesium sulphate and the solvent was evaporated off *in vacuo* to give the crude product as a dark-brown syrup. The syrup was purified by dry flash-column chromatography on silica gel, with petroleum ether (40-60 °C) containing up to 10% ether as the eluent (see ref. 85). Bis-(*p*-ethynylphenyl) ether has an R_f value of *ca.* 0.7 in this solvent system and the chromatography was stopped when a solvent fraction no longer displayed this value. The alkyne is recognisable by its infrared spectrum, with the alkynic C-H stretching frequency a sharp peak at 3274 cm^{-1} and the C≡C absorption a weak peak at *ca.* 2110 cm^{-1}.

Yield 1.12g (43%), m.p. 71°C (lit.[105], 77-77.5°C)

δ_H 3.04 (2H, s, alkyne-H), 7.42 and 6.91 (8H, AA'BB', Ar-H)

Formation of 4,4'-diethynylbiphenyl (**37**)

Phosphoryl chloride (18.6 ml, 0.2 mol) was added dropwise, with stirring, over 30 minutes to dry *N,N*-dimethylformamide (100 ml).under an argon atmosphere. The mixture was stirred for another thirty minutes, then 4,4'-diacetylbiphenyl (**2**) (11.9g, 0.05 mol) was added at once to the orange/red solution. The mixture was then heated to 60°C and stirred for 5h while still under argon. The solution was cooled to room temperature and poured into ice/water (500 ml), the dark solution formed then being neutralised (pH 7) by gradual addition of solid sodium hydrogen carbonate.

N.B. Care must be taken when adding the sodium hydrogen carbonate, as the mixture effervesces vigorously and rapid addition can result in frothing over of the liquid.

The neutral solution was set aside in a refrigerator overnight. The bis-(β-chlorocinnamaldehyde) formed was then filtered off, washed with water (2 x 150 ml), dissolved in dichloromethane (450 ml), washed with dilute brine (3 x 100 ml) and then dried over magnesium sulphate. The solvent was removed *in vacuo* to give the cleaned

product (8.8g, 53%), which was taken forward to the next preparative step without any further purification.

A solution of sodium hydroxide (1.92g, 0.048 mol) in dioxan:water (90 ml, 3:2) was heated to 80°C, and the bis-(β-chlorocinnamaldehyde) (3.97g, 0.012 mol) was then added in one portion. The mixture darkened rapidly and was left stirring at 80°C for 30 minutes, cooled to room temperature and then poured into dilute brine solution (250 ml). This solution was then extracted with dichloromethane (1 x 150 ml, then 3 x 75 ml), and the combined extracts were dried over magnesium sulphate. The solvent was evaporated off *in vacuo* to give the crude product as a dark-brown syrup. The syrup was purified by dry flash-column chromatography on silica gel, with petroleum ether (40-60 °C) containing up to 10% ether as the eluent. 4,4'-diethynyl-biphenyl has an R_f value of *ca.* 0.7 in this solvent system and the chromatography was stopped when a solvent fraction no longer displayed this value. The alkyne is recognisable by its infrared spectrum, with the alkynic C-H stretching frequency a sharp peak at 3268 cm^{-1} and the C≡C absorption a weak peak at *ca.* 2110 cm^{-1}.

Yield 0.65g (27%), m.p. 158-161°C (lit.[106], 166-166.5°C)

δ_H 3.13 (2H, s, alkyne-H), 7.10-7.86 (8H, m, Ar-H)

Formation of *p*-diethynylbenzene (38)

Phosphoryl chloride (18.6 ml, 0.2 mol) was added dropwise, with stirring, over 30 minutes to dry *N,N*-dimethylformamide (100 ml).under an argon atmosphere. The mixture was stirred for another thirty minutes, then *p*-diacetylbenzene (3) (8.1g, 0.05 mol) was added at once to the orange/red solution. The mixture was then heated to 60°C and stirred for 5h while still under argon. The solution was cooled to room temperature and poured into ice/water (500 ml), the dark solution formed then being neutralised (pH 7) by gradual addition of solid sodium hydrogen carbonate.

N.B. Care must be taken when adding the sodium hydrogen carbonate, as the mixture effervesces vigorously and rapid addition can result in frothing over of the liquid.

The neutral solution was put in a refrigerator overnight. The bis-(β-chlorocinnamaldehyde) formed was then filtered off, washed with water (2 x 150 ml), dissolved in dichloromethane (450 ml), washed with dilute brine (3 x 100 ml) and then dried over magnesium sulphate. The solvent was then removed *in vacuo* to give the cleaned product (5.4g, 42%), which was then taken forward to the next preparative step without any further purification.

A solution of sodium hydroxide (1.92g, 0.048 mol) in dioxan:water (90ml, 3:2) was heated to 80°C, and the bis-(β-chlorocinnamaldehyde) (3.06g, 0.012 mol) was then added in one portion. The mixture darkened rapidly and was left stirring at 80°C for 30 minutes, cooled to room temperature and then poured into dilute brine solution (250 ml). This solution was then extracted with dichloromethane (1 x 150 ml, then 3 x 75 ml), the combined extracts were dried over magnesium sulphate and the solvent was evaporated off *in vacuo* to give the crude product as a dark-brown syrup. The syrup was purified by dry flash-column chromatography on silica gel, with petroleum ether (40-60°C) containing up to 10% ether as the eluent. *p*-Diethynylbenzene has an R_f value of *ca.* 0.7 in this solvent system and the chromatography was stopped when a fraction of eluate no longer gave rise to a spot with this value. The alkyne is recognisable by its infrared spectrum, with the alkynic C-H stretching frequency a sharp peak at 3262 cm^{-1} and the C≡C absorption a weak peak at *ca.* 2110 cm^{-1}.

Yield 0.54g (36%), m.p. 90-92°C (lit.[107], 96.5°C)

$δ_H$ 3.15 (2H, s, 2 x 1H, alkyne-H) and 7.45 (4H, s, 4 x 1H, Ar-H)

Formation of 2,2-bis-(*p*-methoxyphenyl)propane (**40**)

To a solution of sodium hydroxide (20g, 0.5 mol) in water (200 ml), bisphenol A (**39**) (57g, 0.025 mol) was added. The mixture was stirred and cooled to 10°C in an ice-bath. Dimethyl sulphate (63g, 0.5 mol) was added dropwise over 1h while stirring the mixture vigorously. The solution was then heated and refluxed for 4h to ensure complete methylation. The solution was then cooled, water was added (250 ml) and the

mixture was extracted with ether (3 x 150 ml). The combined ether extracts were then washed with water (2 x 150 ml) then dried over magnesium sulphate. The ether was then removed *in vacuo* and the residual syrup was sucked dry on a water-pump and left in a refrigerator overnight. The solid formed was then recrystallised from methanol.

Yield 25.2g (39%), m.p. 56-57°C (lit.[86], 59-61.5°C)

δ_H 1.72 (6H, s, CH$_3$-C), 3.84 (6H, s, CH$_3$-O), 6.88 and 7.23 (8H, AA'BB', Ar-H)

Attempted formation of 2,2-bis-(3-acetyl-4-hydroxyphenyl)propane (42)

(a) Acetyl chloride (37 ml, 18.8g, 0.073 mol) was added to a solution of 2,2-bis-(*p*-methoxyphenyl)propane (40) in dry 1,2-dichloroethane (150 ml) and the mixture was stirred at 0°C for 2h. Aluminium chloride (71.4g, 0.53 mol) was added over 2h and then the mixture was heated to 70°C. At 30°C the mixture started to thicken and at 70°C a thick brown sludge was formed. After 2h at 70°C the mixture was cooled down and then poured into ice/conc. HCl (400 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 x 100 ml). The organic layers were combined, washed with water (200 ml) and dried over magnesium sulphate. The solvent was then removed *in vacuo* and the product was recrystallised from methanol. Upon analysis it was found that the methylated (41) and demethylated (42) product were present in approximately equal amounts.

The reaction was repeated, with the mixture being kept at ambient temperature for 24h. The results from this showed no significant improvement.

(b) Aluminium chloride (26.9g, 0.2 mol) was added to dry dichloromethane (200 ml) and the mixture stirred at 0°C. Acetyl chloride (15.7g, 0.2 mol) was then added slowly, with stirring, at such a rate as to ensure that the temperature did not exceed 5°C. A solution of 2,2-bis-(4-methoxyphenyl)propane (40) (17.2g, 0.067 mol) in dry dichloromethane (50 ml) was added dropwise with stirring. Upon complete addition the pale green solution was left at 0°C for 4h and then at room temperature

overnight. The solution was then poured into ice / conc. HCl (40 ml) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 x 100 ml) and the combined organic layers were washed with water (2 x 100 ml) and then dried over magnesium sulphate. The solvent was removed *in vacuo*, and the product recrystallised from ethanol. Upon analysis (^{1}H n.m.r.) it was seen that the amount of the desired demethylated compound (**42**) accounted for approximately 70% of the product.

The reaction was attempted again, varying the length of reaction time (1-3 days), but the best results were obtained by allowing the mixture to stir for 4h at 0°C and then heating the solution under reflux for 4h. This gave a product containing approximately 85% of the desired demethylated compound **42** but still 15% of the methylated compound **41**.

Formation of 2,2-bis-(3-bromo-4-hydroxyphenyl)propane (**44**)

Bromine (16.0g, 0.1 mol) in chloroform (30 ml) was added dropwise with stirring and cooling over 2h to a solution of bisphenol A (**39**) (11.4g, 0.05 mol) in a mixture of chloroform (60 ml) and ether (70 ml). The reaction was then left stirring at ambient temperature for 4h and then the solvents were removed on the rotary evaporator. The resinous product formed was then left overnight in the refrigerator. The solid formed was then recrystallised from a 50:50 mixture of ether:petroleum.

Yield 13.6g (70%), m.p. ....(lit.[90],76-78°C)

δ_H 1.54 (6H, s, CH$_3$), 6.82 (2H, d, 5-H), 6.92 (2H, dd, 6-H), 7.25 (2H, dd, 2-H), 7.61 (2H, br, OH)

Formation of thiocarbohydrazide (**46**)

In a 1-litre 3-necked flask, carbon disulphide (60 ml, 1 mol) was added dropwise to a vigorously stirred solution of 80% hydrazine hydrate (300 ml; 4.94 mol) in water (100 ml) with the temperature monitored to ensure that it did not exceed 45°C. Upon complete addition the mixture was refluxed for 45 minutes, then left for 1h in an ice/water bath. The resulting precipitate was then filtered off and the mother liquor

returned to the flask and refluxed again for another 45 minutes and then allowed to cool overnight in an ice/water bath. The precipitate formed was filtered off, and the two solid products were combined and washed with ether. The resulting product was recrystallised from *ca.* 500ml of boiling water (acidified with a few ml of conc. HCl), then filtered and finally air-dried for 36h.

Yield 59.2g (56%), m.p. 168-169.5°C (lit.[92(a)], 171°C)

Formation of trithiocarbodiglycolic acid(**48**)

In a 300 ml 3-necked round-bottomed flask with a stirrer, gas inlet and outlet tube attached, a solution of potassium hydroxide (63g, 0.96 mol in 100 ml water) was added. The solution was cooled and stirred in an ice bath, then hydrogen sulphide was bubbled through for 4h, during which time the solution turned from colourless to dark green.

N.B. It was important to ensure that a trap with an oxidising agent was attached to the gas outlet tube to trap excess hydrogen sulphide. In this case aqueous potassium permanganate was used, with a colour change of purple to pink showing the reaction to be complete.

The solution was then poured into a 2-litre 3-necked flask fitted with a stirrer, gas inlet tube, reflux condenser and a thermometer reaching into the liquid. The 300ml flask was rinsed with 50ml water and the rinsings were added to the solution. Whilst stirring the solution, potassium hydroxide (63g, 0.96 mol) was added and allowed to dissolve. The flask was then flushed out with argon and at 30°C carbon disulphide (60ml, 1 mol) was added at once. The mixture was stirred vigorously for 2h, with the reaction being under argon and the temperature varying between 35-38°C. The resulting dark red solution was then stoppered and cooled in an ice/water bath.

Chloroacetic acid (189g, 2 mol) in water (300 ml) was neutralised (litmus paper), using a solution of potassium hydroxide (135g, 2.1 mol) in water (300 ml). The resulting potassium chloroacetate solution was placed in a dropping funnel and added, with stirring, to the potassium thiocarbonate solution, at such a rate that the temperature did not exceed 40°C. It was observed that, with this addition, the colour in

the reaction flask changed from deep red to dirty yellow/orange. Upon complete addition, the flask was placed in an ice/water bath and allowed to stir until the temperature in the flask dropped to room temperature. Then conc. hydrochloric acid (200ml) was added over 2h, with the temperature kept constantly below 20°C by the ice/water bath. The solution was then left stirring at room temperature overnight and the brilliant yellow precipitate formed was filtered off and washed with water (2 x 200 ml) and then dried in a vacuum desiccator over calcium chloride for two days, with the lumps of product being broken up to quicken the drying process.

Yield 143.1g (65%), m.p. 169-172°C (lit.[92(c)] 169-174°C)

Formation of tetrahydro-1,2,4,5-tetrazine-3,6-dithione (**47**)

Thiocarbohydrazide (**46**) (10.6g, 0.1 mol) was dissolved in boiling water (150 ml) and then filtered into a stirred solution of thiocarbodiglycolic acid (**48**) (22.6g, 0.1 mol) in 200ml of 1M sodium hydroxide solution. The resultant yellow solution was then left in the refrigerator for three days, then at room temperature for one day. The solution was then filtered and a pale yellow precipitate was obtained. This precipitate was washed with water (50 ml) and then dried *in vacuo* with an oil pump. The filtered reaction mixture was left in in a fume cupboard for five days and a second crop of product was obtained and purified as previously described.

Yield 7.1g (48%), m.p. 173-175°C (lit.[92 (b)] 176°C)

Formation of dihydro-3,6-bis(methylthio)-1,2,4,5-tetrazine (**49/50**)

Under argon, a solution of methyl iodide (7.1g, 0.05 mol) in 95% ethanol (25 ml) was added to an ice-cooled solution of tetrahydro-1,2,4,5-tetrazine-3,6-dithione (**47**) (3.7g, 0.025 mol) in 1M sodium hydroxide solution (50 ml). The mixture was left stirring overnight at room temperature and a precipitate was seen to be present. As the reaction proceeded, the colour changed from grey to brown/red. The solution was filtered and the rose coloured precipitate was washed with water and then dried in a vacuum desiccator over calcium chloride.

Yield 2.32g (53%), m.p. 191-193°C (lit.[92(b)] 192-193°C)

Formation of 3,6-bis(methylthio)-1,2,4,5-tetrazine (**45**)

To a hot solution (ca. 60°C) of dihydro-3,6-bis(methylthio)-1,2,4,5-tetrazine (**49/50**) (4.05g, 0.023 mol) in ethanol (200 ml) was added 2M ferric chloride (23 ml). The resulting red solution was allowed to stand for 1h, diluted with water (150 ml) and then left chilling in the refrigerator overnight. The deep red precipitate formed was filtered off to give 3.66g (91%), m.p. 80-81°C. Recrystallisation of the product from hexane gave brilliant red-coloured powdery crystals.

Yield 3.26g (82%), m.p. 82-84°C (lit.[92(b)] 83.5-84°C)

Formation of 3-hydrazino-6-(methylthio) -1,2,4,5-tetrazine (**51**)

To a stirred solution of 3,6-bis(methylthio)-1,2,4,5-tetrazine (**45**) (5.0g, 0.0287 mol) in ethanol (250 ml), a solution of hydrazine hydrate (1.62g, 0.0324 mol) in ethanol (5 ml) was added dropwise at room temperature. After 4h the precipitate formed was filtered and the filtrate was concentrated *in vacuo* to half its volume to give a second crop of product. The two crops were were added together, after checking their purity on t.l.c. (chloroform : methanol, 20:1). A small amount of the product was recrystallised from ethanol.

Yield 2.75g (61%), m.p. 135-137°C (lit.[93], 136-138°C)

δ_H (d$_6$-DMSO) 2.60 (3H, s, CH$_3$), 4.48 (2H, br, NH$_2$) and 9.28 (1H, br, NH)

Formation of 3-amino-6-(methylthio)-1,2,4,5-tetrazine (**52**)

To a stirred suspension of 3,6-bis(methylthio)-1,2,4,5-tetrazine (**45**) (1.94g, 0.011 mol) in methanol (50 ml), a solution of ammonia (0.0055 mol/ml) in methanol (6 ml) was added dropwise at room temperature. After 2h all the solid had dissolved and the reaction had reached completion as shown by t.l.c. (benzene : ethyl acetate : acetic acid, 34:15:1). The solution was concentrated *in vacuo* to give an orange solid which was then recrystallised from ethanol.

Yield 1.02g (65%), m.p. 142-144.5°C (lit.[93], 143-146°C)

δ_H (d$_6$-DMSO) 2.60 (3H, s, CH$_3$) and 7.55 (2H, br, NH$_2$)

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