University of St Andrews

The Synthesis and Inverse Electron Demand Diels-Alder Reaction of Bis-1,2,4-triazines

Being a thesis by

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Submitted for the degree of Doctor of Philosophy in the
Faculty of Science of the University of St. Andrews

March 1995

Declaration

I, Gillian Anne McLean, 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 1991, and that it has not been accepted in any previous application for any Higher Degree or professional qualification.

March 1995   Signed.

I hereby certify that Gillian Anne McLean has fulfilled the Regulations appropriate to the Degree.

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Dedication

I would like to dedicate this thesis to my mother and father.

ABSTRACT

Chapter 1 (Introduction)

This chapter begins with a description of the uses and criteria necessary for polymers to be considered as being 'high performance' and the use of the Diels-Alder reaction in polymer synthesis. A review of the inverse electron demand Diels-Alder reaction of heterocycles containing two or more nitrogen atoms follows, with particular emphasis on the 1,2,4-triazine molecule. Methods of 1,2,4-triazine formation are then discussed and previously reported methods for bis-1,2,4-triazine formation are reviewed.

Chapter 2 (Results and Discussion)

This chapter develops the ideas formed in Chapter 1 to seek a synthetic route to novel polymers containing stable heteroaromatic rings. A variety of bis-dienes and bis-dienophiles were synthesised and attempts at inverse electron demand Diels-Alder reactions were carried out.

Two synthetic routes to novel 5,5'-linked bis-1,2,4-triazines have been developed. The first involved the oxidation of diacetyl aromatics to bis-glyoxals and their subsequent conversion into 3,3'-bis(methylsulphanyl)-5,5'-arylenebis-1,2,4-triazines by reaction with S-methylthiosemicarbazide. The methylsulphanyl groups were then oxidised to the corresponding methylsulphinyl and methylsulphonyl compounds. The second route involved coupling reactions of preformed mono-1,2,4-triazines to a central 'core'. Synthetic routes to diethynyl-aromatics and bis-enamines have also been investigated and all attempts at Diels-Alder reactions of the bis-1,2,4-triazines with these compounds in intermolecular Diels-Alder reactions have proved unsuccessful so far. Synthetic routes to bis-(o-ethynylphenols) have also been investigated for use in intramolecular Diels-Alder reaction attempts.

Chapter 3 (Experimental)

This Chapter details the synthetic procedures used and the Bibliography and Appendix follows.

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Chapter 1
Introduction

1. **High performance polymers**

The requirements of modern technology, including those related to the aerospace industry, place increasing demands on polymers to withstand long-term exposure to temperatures exceeding 200°C.

The major criteria necessary for a polymer to be of a 'high performance' nature are as follows:

- The chemical bonds of the polymer backbone must withstand high temperatures, even after long ageing.

- The molecular motions within the polymer backbone must be restricted, thus raising the melting point and/or glass transition temperature.

As the temperature of a polymer is lowered, a point known as the glass transition temperature[1] is reached where polymeric materials undergo a marked change in properties, associated with the virtual cessation of local molecular motion. Below the glass transition temperature, amorphous polymers have many of the properties associated with ordinary glasses, including hardness, stiffness, brittleness and transparency. A polymer's melting point or glass transition temperature can be raised by, for example, increasing the stiffness of individual chains by using spacers containing multiple bonds or ladder-type systems (whose structure is so fixed that a few bonds being broken will not sever the chain). For example, the ladder polymer **1** is formed[2] from the heating of polyacrylonitrile **2** first to 200°C, followed by heating the red product **3** to 350°C to obtain a brittle black material. Further heating of this type of ladder polymer at extreme temperatures (1500–3000°C) results in the elimination of all elements other than carbon to leave a 'carbon fibre' with graphitic crystalline structure which is of great strength.
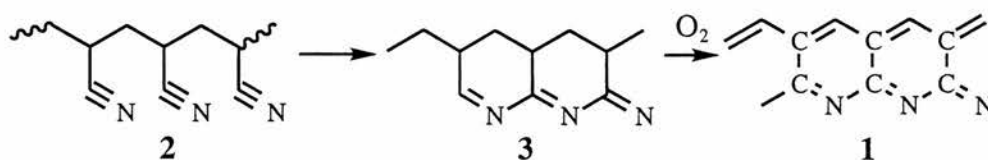
Other influences which may improve high temperature stability are partial crystallinity of the polymer, cross-linking of the chains and restriction of molecular motion by π-bonding or dipole/dipole interactions. For example, poly(m-phenylene isophthalamide) **4**,[3] commercially known as Nomex (Du Pont), which is synthesised from isophthaloyl chloride **5** and m-phenylenediamine **6** is an aromatic polyamide with use mainly in flame-resistant clothing. It has a relatively high melting point of 380–390°C, has mechanical properties which can withstand high temperatures and shows little change in insulation properties up to around 200°C. Kevlar (Du Pont)[4] (the *para*-linked analogue) does not melt and is therefore even more useful particularly in bullet-proof clothing, particularly due to its outstanding strength-weight ratio.
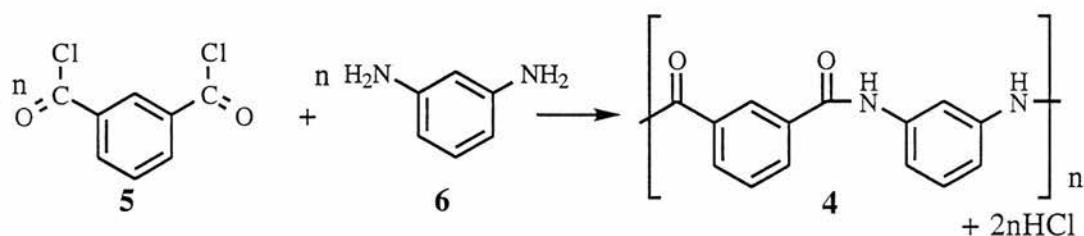
In contrast, Nylon 66 **7**,[5] an aliphatic equivalent, is made from hexamethylenediamine **8** and adipic acid **9**, has a much less rigid backbone, melts at around 264°C, and is therefore less useful for high temperature purposes.
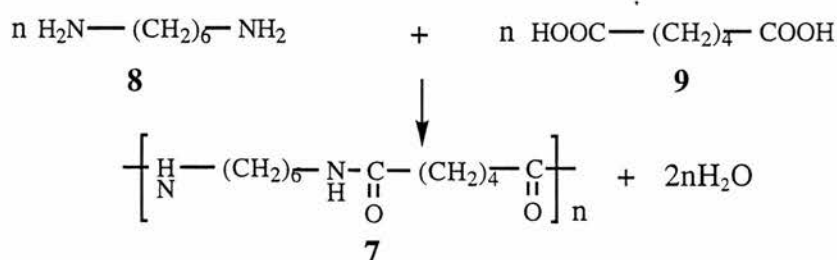
According to Billmeyer,[6] one high temperature polymer which found widespread use in electrical components is shown below. This polyphenylene oxide polymer **10**, for example, when R=CH$_3$ is stable at temperatures in excess of 200°C.

10
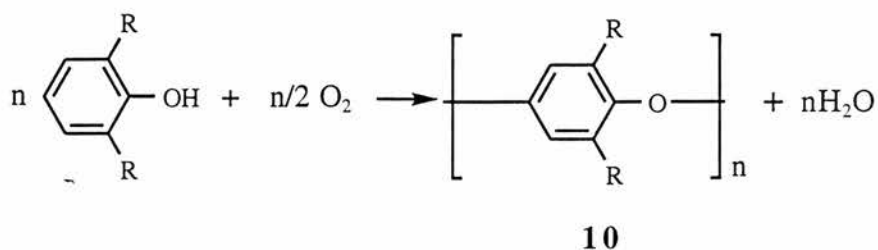
Thermally stable aromatic/heteroaromatic polymers have found widespread interest in 'high performance' chemistry due to their inherent resistance towards oxidation. It is desirable that functional groups on the rings and any atoms or groups joining the rings should also be resistant to oxidation and aid in the spatial packing by possessing planar or linear characteristics. Tetrahedral linking groups (e.g. SO_2) result in a weakening of the polymer, as the polymer chains are then unable to pack together so effectively and the polymer is therefore more susceptible to solvent uptake.

Most aromatic/heteroaromatic polymers reported in the literature are made from monomers which already have aromatic/heteroaromatic units present and the polymerisation step involves a simple functional group transformation (e.g. nucleophilic or electrophilic aromatic substitution). In the example shown below, PEEK (PolyEtherEtherKetone) **11**[7] is synthesised by the reaction of hydroquinone **12** and 4,4'-difluorobenzophenone **13** in the presence of potassium and sodium carbonates.

13   **12**

11
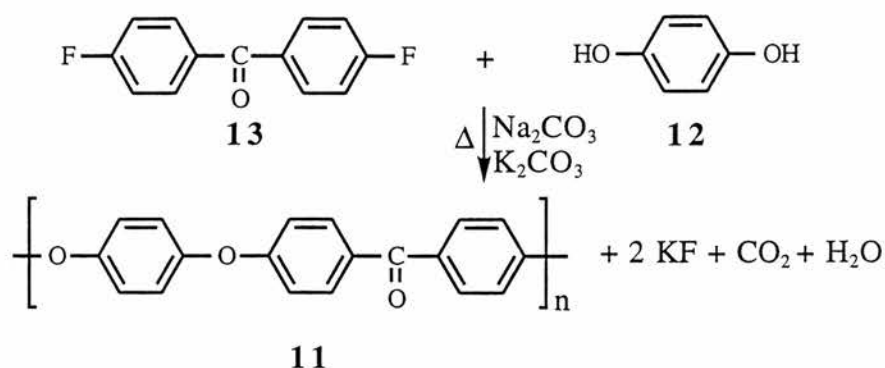
Syntheses of aromatic/heteroaromatic polymers which have, as the polymerisation step, the **formation of the aromatic/heteroaromatic ring itself** have been less

4

thoroughly explored. In the benzene series this is perhaps not surprising because of the large variety of benzene derivatives which are available and also because methods for the synthesis of benzene rings have not been widely developed. Given the range and diversity of methods available for the synthesis of heteroaromatic ring systems it is perhaps surprising that more polymers containing a heteroaromatic backbone have not been reported. The formation of a heteroaromatic group in the polymerisation step[8] can be exemplified by the polycondensation of 2,6-pyridinediyl dihydrazidine **14** with 4,4'-oxybis(phenylglyoxal) **15**[9] to give poly-1,2,4-triazines **16**. Poly(arylene-1,2,4-triazines), prepared from diamidrazones and dibenzils, exhibit solubility characteristics unique for all aromatic heterocyclic polymers, being soluble in chloroform at concentrations as high as 30% solids. However, significant degradation occurred when aged for only 50 hours at 290°C as indicated by weight losses which were greater than 13%.
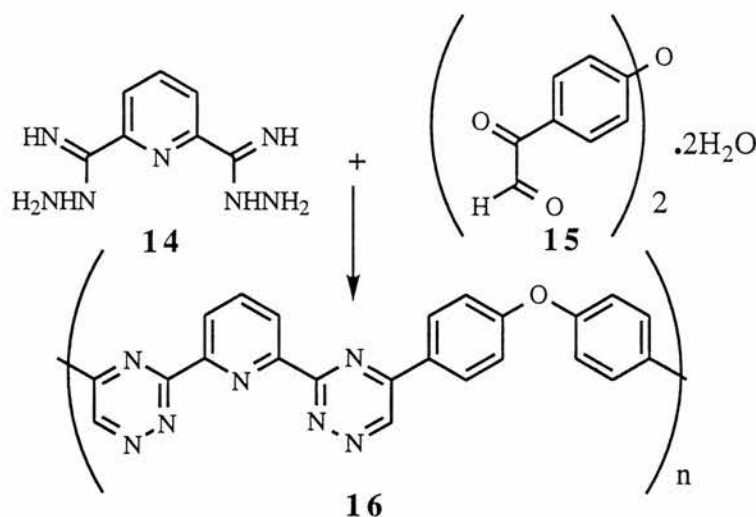
The formation of an aromatic/heteroaromatic ring can be easily achieved in certain cases by the use of the Diels-Alder reaction.

2. **The Diels-Alder reaction**

The Diels-Alder reaction is one of the most widely used reactions in synthetic organic chemistry. The diagram below describes a simple Diels-Alder reaction of a conjugated diene **17** with a simple alkene **18** to give a 6-membered ring **19**.
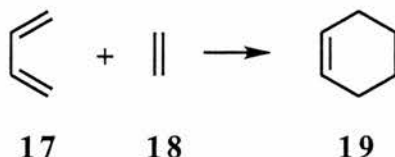
The Diels-Alder reaction is a thermal cycloaddition[10] where the 4π component is a conjugated diene and the 2π component is known as a dienophile. The cycloaddition is reversible and the reverse process is known as a retro Diels-Alder reaction. Initial studies defined the stereochemistry and regiochemistry, suggesting the mechanism to be a concerted bimolecular process. The diagram below describes the alternative mechanisms which were proposed:[11-13] either a one step reaction involving a concerted mechanism or a two step reaction sequence involving a biradical **20** or zwitterion intermediate **21**.
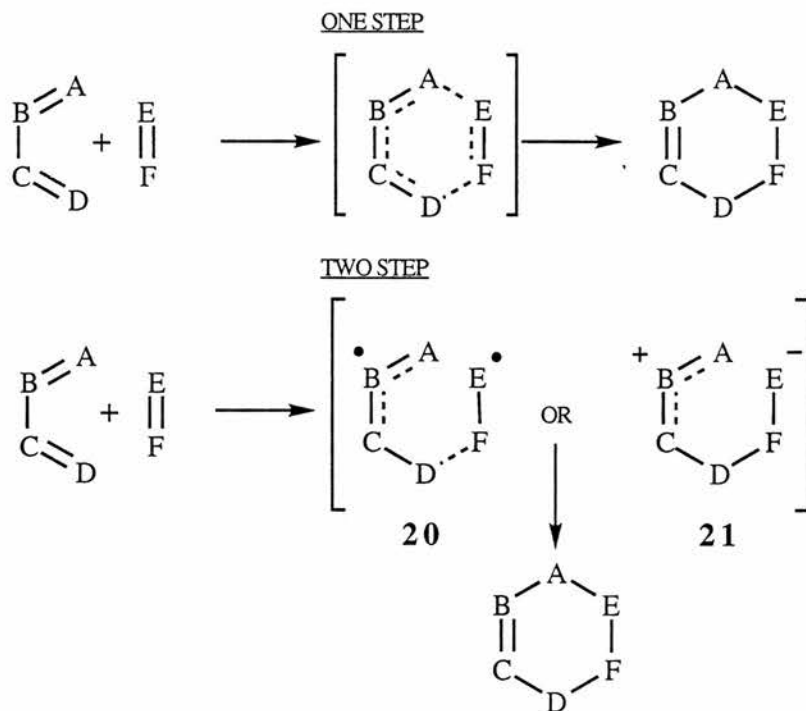
The search for the simplest possible description of regioselectivity and reactivity led to the application of frontier orbital theory.[14-16] The Diels-Alder reaction may be classified into three reaction types,[17] according to the possible interactions of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of the two reacting species. The three types of cycloaddition are as follows:

- NORMAL ELECTRON DEMAND ($HOMO_{diene}$ controlled) Diels-Alder reaction.

- NEUTRAL Diels-Alder reaction (in which both HOMO-LUMO interactions must be considered).

- INVERSE ELECTRON DEMAND ($LUMO_{diene}$ controlled) Diels-Alder reaction.
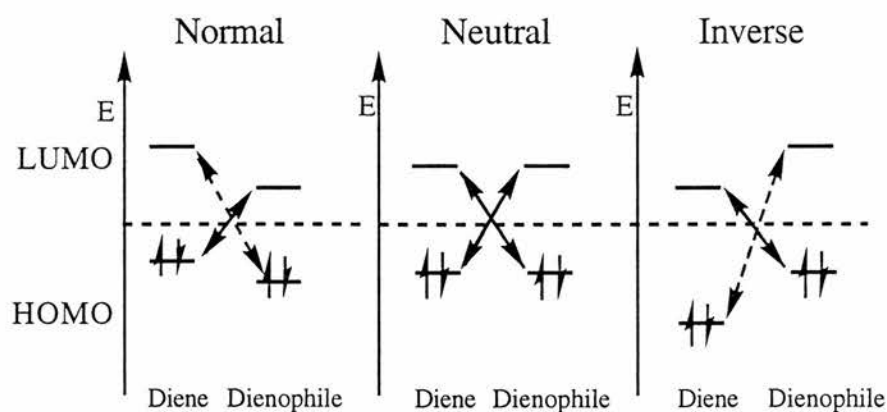
The rate of a Diels-Alder reaction has been shown to be related to the size of the lower HOMO-LUMO energy separation of the reacting diene/dienophile pair[18](i.e. $LUMO_{dienophile}$–$HOMO_{diene}$ or $LUMO_{diene}$–$HOMO_{dienophile}$). Substituents attached to the 4π and/or 2π components of Diels-Alder reactions can be manipulated in such a way that the magnitude of the smaller HOMO-LUMO energy separation is lessened, giving reactions which occur under milder reaction conditions [temperature, pressure and reaction time].

A 'normal' Diels-Alder reaction employs an electron-rich diene (which serves to increase the energy of $HOMO_{diene}$) and an electron-deficient dienophile (which serves to decrease the energy of $LUMO_{dienophile}$). Electron-donating substituents on the diene and

electron-withdrawing substituents on the dienophile increase the reaction rate.

For 'inverse electron-demand' Diels-Alder reactions the dominant molecular orbital interaction is between $LUMO_{diene}$ and $HOMO_{dienophile}$. Such a Diels-Alder reaction involves an electron-deficient diene (decreased energy of $LUMO_{diene}$) and an electron-rich dienophile (increased energy of $HOMO_{dienophile}$). Electron-withdrawing substituents on the diene and electron-donating groups on the dienophile result in an increased reaction rate.

A 'neutral' Diels-Alder reaction is one in which both HOMO-LUMO separations are of similar magnitude. Electron withdrawing/donating substituents either lower or raise both HOMO and LUMO; each type of substituent will strengthen one HOMO-LUMO interaction but weaken the other.

The Diels-Alder reaction is a reversible reaction, and the retro Diels-Alder reaction may be brought about by, for example, heating the adduct. Therefore, in order to obtain an essentially irreversible reaction, there must be a driving force towards product formation such as, for example, the expulsion of a small molecule from the initial adduct. If such an expulsion results in the formation of a stable aromatic ring this driving force is greatly increased.

Among the "classical" Diels-Alder reactions which give aromatic rings the best known are those involving the reaction of an α-pyrone 22 with an alkyne.[19] 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.
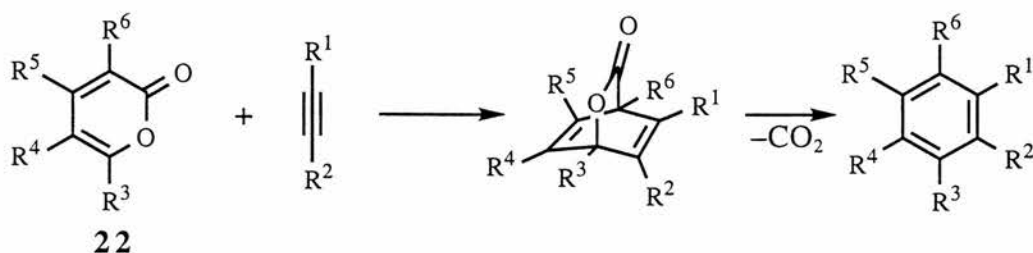
Tetraphenylcyclopentadienone 23 ("tetracyclone") reacts similarly with a simple alkyne 24,[20] to give 25, where the small molecule eliminated is carbon monoxide.
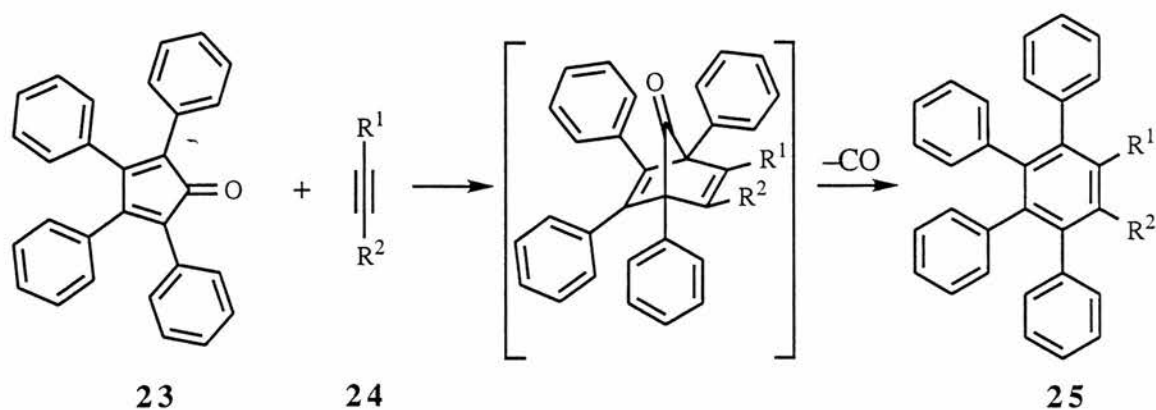
3. The Diels-Alder reaction in polymer synthesis

There are many reports of the use of the Diels-Alder reaction for preparing polyimides **26**,[21,22] by for example the reaction scheme shown below. Otherwise, however, there are few examples of its application in aromatic or heteroaromatic polymer synthesis.
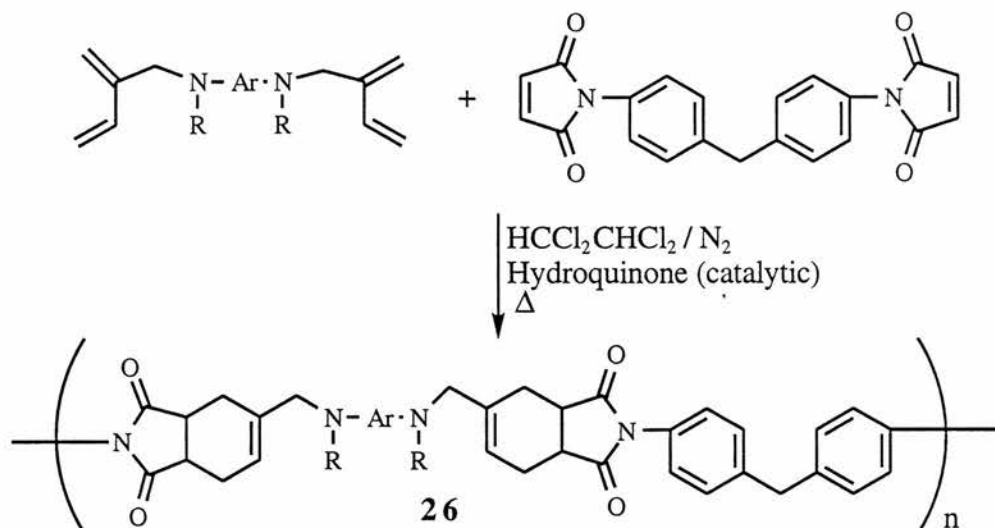
This may, in part, be due to the reaction being reversible, creating polymers whose thermal stability may be limited. However, although the loss of a small molecule (e.g. carbon monoxide, nitrogen) from the initial adduct to give a stable aromatic ring should result in a more stable polymer, void formation in the cured polymer may result. Volatile by-products are responsible for problems in the fabrication of objects where high

mechanical strength is required.[23]

The best known polymer-forming reactions which involve loss of a small molecule from the initial cycloadduct are based on the reactions of alkynes with tetraphenylcyclopentadienone ('tetracyclone') or α-pyrones. Extension of these reactions in a step-growth polymerisation reaction has been studied[24] with the use of bis-(cyclopentadienones),[25] bis-(α-pyrones)[26] or bis-(thiophene dioxides)[27] as the dienes. The Diels-Alder reaction of bis-tetracyclones 27 and m- 28 and p- 29 diethynylbenzenes affords polymers 30.[28]

$$X = (CH_2)_n, S, O, SO_2$$
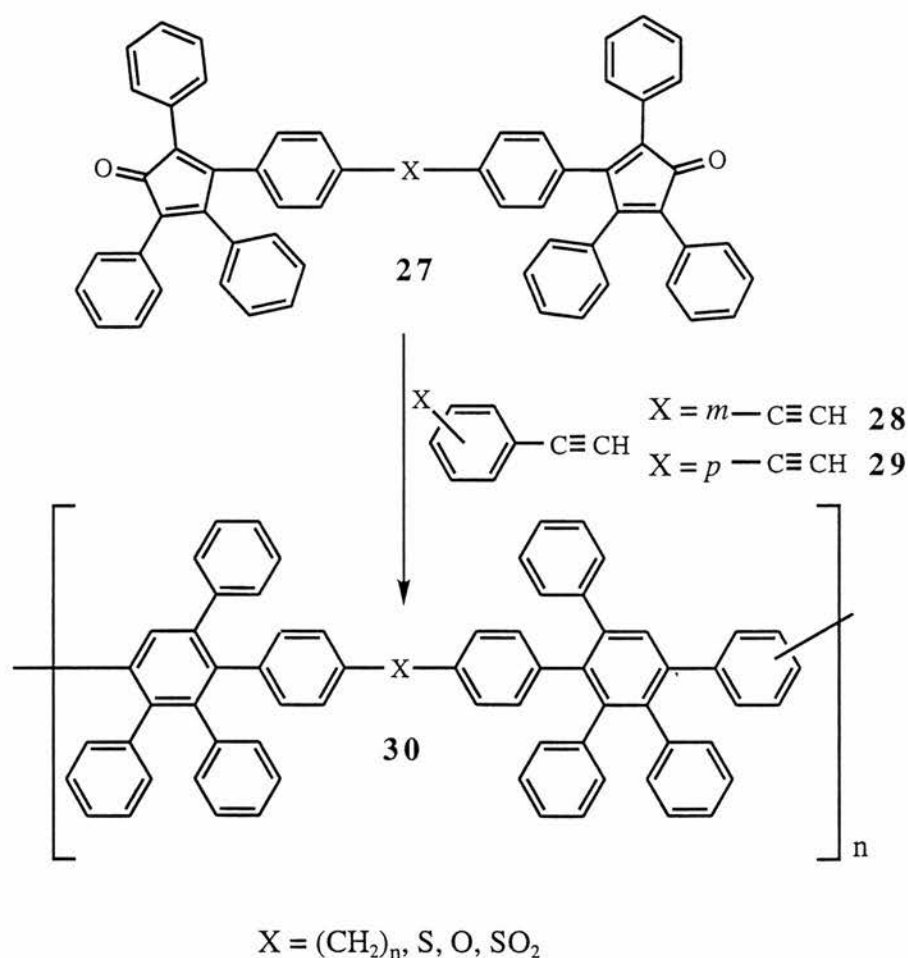
These polymers are colourless, possess good thermal stability in the air at temperatures exceeding 350°C and are appreciably soluble in common organic solvents. The polymers are however of low molecular weight and have poor mechanical strength. Several of these polymers,[29] when pyrolysed at 750°C under nitrogen, give benzene,

biphenyl and other higher boiling hydrocarbons as volatile products (30% total weight).

Bis-α-pyrones **31** also react with *p*-diethynylbenzene **32**[30] by a Diels-Alder reaction followed by elimination of CO_2 to give a quantitative yield of mainly *para*-linked **33**.
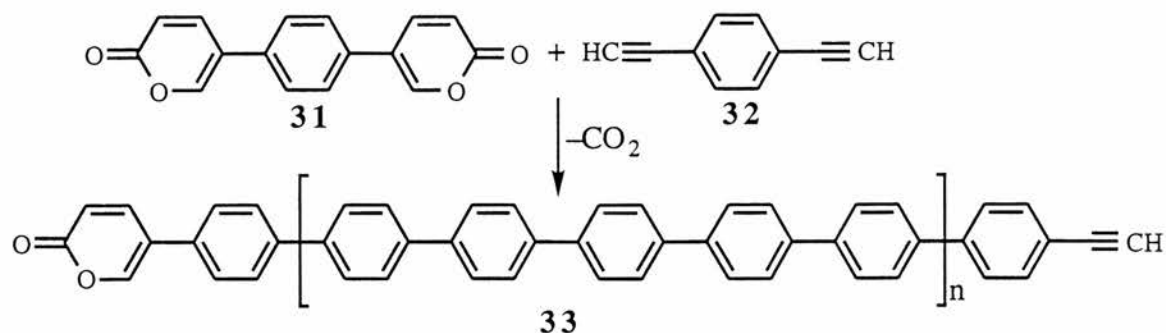
As has been discussed, a double Diels-Alder reaction has been successfully used for the synthesis of polymers. This current research concerns the synthesis of heterocyclic polymers starting from bis-azadienes.

4. The inverse electron demand Diels-Alder reaction in polymer synthesis

Although there are reports of the incorporation of azadienes into polymer chains, there are no published accounts of the synthesis of polymers using the inverse electron-demand Diels-Alder reaction of bis-azadienes and bis-dienophiles with expulsion of a small molecule from the cycloadduct to yield stable heterocyclic polymers. This project has examined the feasibility of such reactions.

5. The intermolecular inverse electron demand Diels-Alder reaction

Heteroaromatic compounds which contain an electron deficient azadiene unit have found widespread use in the inverse electron demand Diels-Alder reaction,[31] particularly in the field of natural product synthesis.

The concept of using heterocycles with three or more nitrogens in the inverse

electron demand Diels-Alder reaction has been extensively researched. Substituted 1,3,5-triazine molecules **34** take part in cycloadditions[32-34] with electron-rich dienophiles. 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.[33]
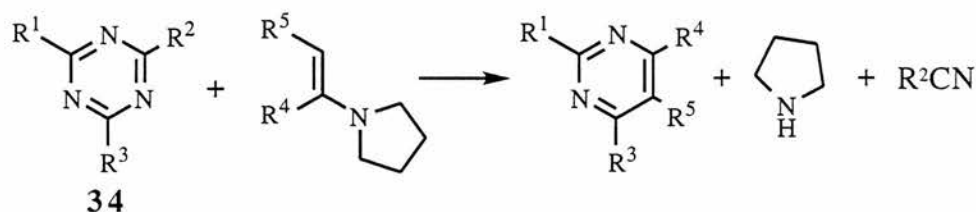
1,2,3-Triazines **35** undergo cycloaddition across N-3 and C-6,[35,36] the dienophile attaching to C-6 of the triazine and the extrusion of molecular nitrogen giving the substituted pyridines.
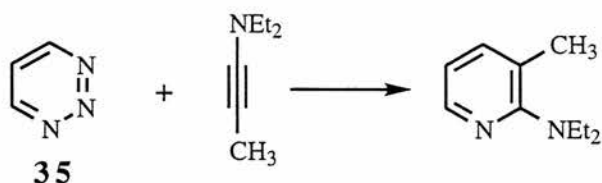
1,2,4,5-Tetrazines, being among the most electron-deficient heterocyclic compounds react readily with a wide variety of multiply-bonded compounds in inverse electron demand Diels-Alder cycloadditions.[37,38] When the tetrazine **36** reacts with an olefin, cycloaddition occurs across C-3/C-6, with expulsion of molecular nitrogen from **37** to give the dihydropyridazine **38**, which then undergoes *in situ* oxidation in air to form the corresponding pyridazine derivative **39**.
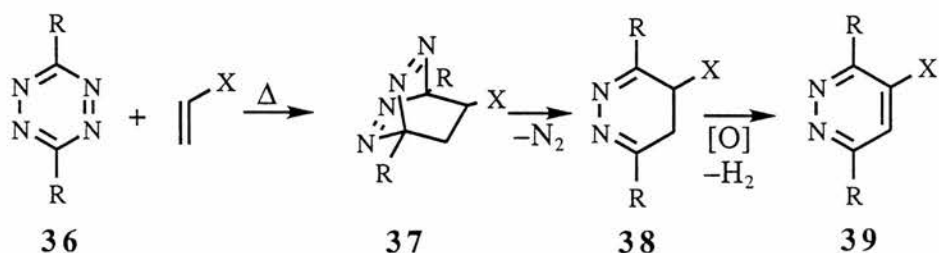
The 1,2,4-triazine molecule is among one of the most widely studied dienes which undergoes such LUMO-$_{diene}$-controlled Diels-Alder reactions.[33,39] The following section describes their reactivity in the intermolecular and intramolecular inverse electron demand Diels-Alder reaction with a wide variety of dienophiles.

6. <u>Intermolecular Diels-Alder reaction of 1,2,4-triazines</u>

The scope of the [4+2] cycloaddition of 1,2,4-triazines with electron-rich dienophiles including enol ethers, enamines, ynamines and strained or reactive olefins has been described.[40,41] Two observed modes of cycloaddition are observed for 1,2,4-triazines. Firstly, electron-rich dienophiles such as 1-(dimethylamino)-1-ethoxy-ethylene **40**[42] add across C-3 and C-6 of the 1,2,4-triazine molecule **41** with a strong preference for the nucleophilic carbon of the dienophile to attach to C-3 of the 1,2,4-triazine **41** to give substituted pyridines **42** via expulsion of molecular nitrogen and ethanol.
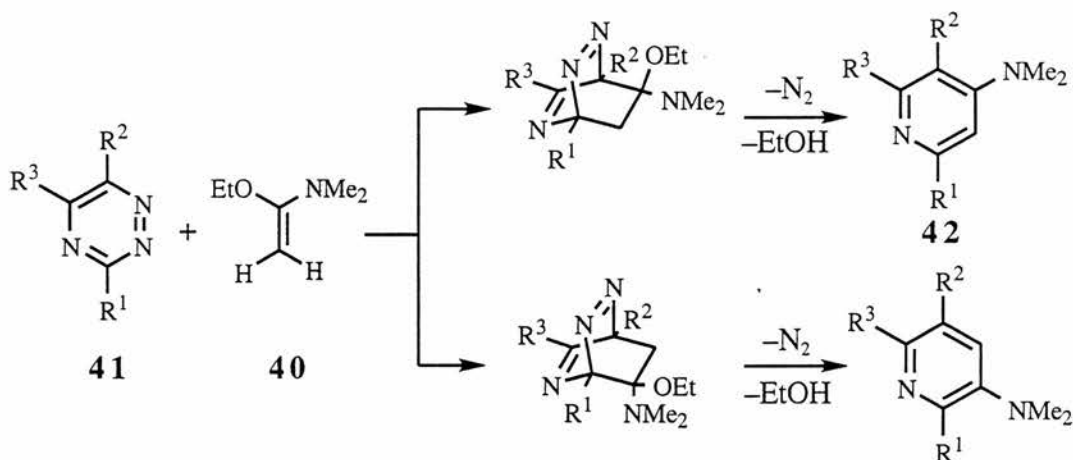
In contrast, the reaction of 1,2,4-triazines **41** with ynamines[43] such as 1-(diethylamino)propyne **43**[44] generally involves a cycloaddition across C-5 and N-2. In this case, the nucleophilic carbon of the dienophile attaches to C-5 of the 1,2,4-triazine, resulting in **44**. If however, the 1,2,4-triazine has a substituent at C-5, cycloaddition may occur across C-3/C-6 with the nucleophilic carbon attaching to C-3 of the 1,2,4-triazine on this occasion to give **45**.
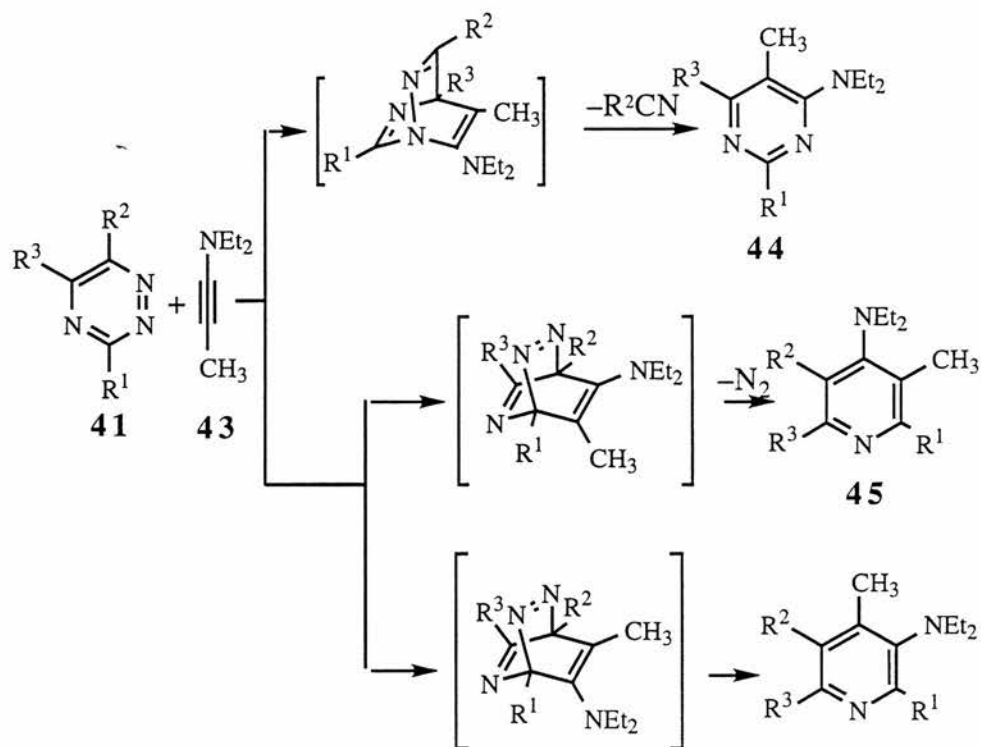
Cycloadditions of enamines to 1,2,4-triazines[45] occur across C-3/C-6 to give 3,4-disubstituted pyridines. In the example shown the sulphide **46** was not sufficiently reactive to undergo a Diels-Alder reaction with the morpholino enamine **47** and gave decomposition products.
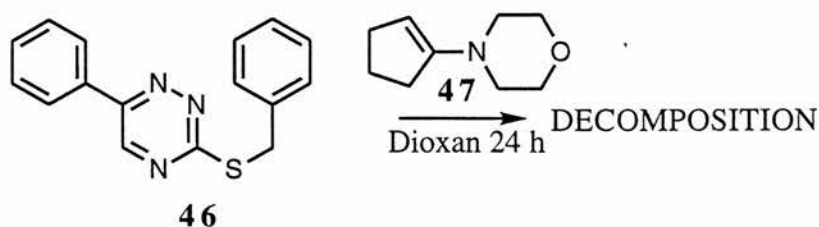
However, on oxidation to the corresponding sulphoxide **48** and sulphone **49** reaction was seen to take place. The addition of glacial acetic acid to the reaction mixture gave 46% of the sulphone cycloadduct **50** and 9% of the sulphoxide cycloadduct **51** The oxidations made the triazines more electron-deficient and thereby increased their reactivity in an inverse electron-demand Diels-Alder reaction with the enamine.
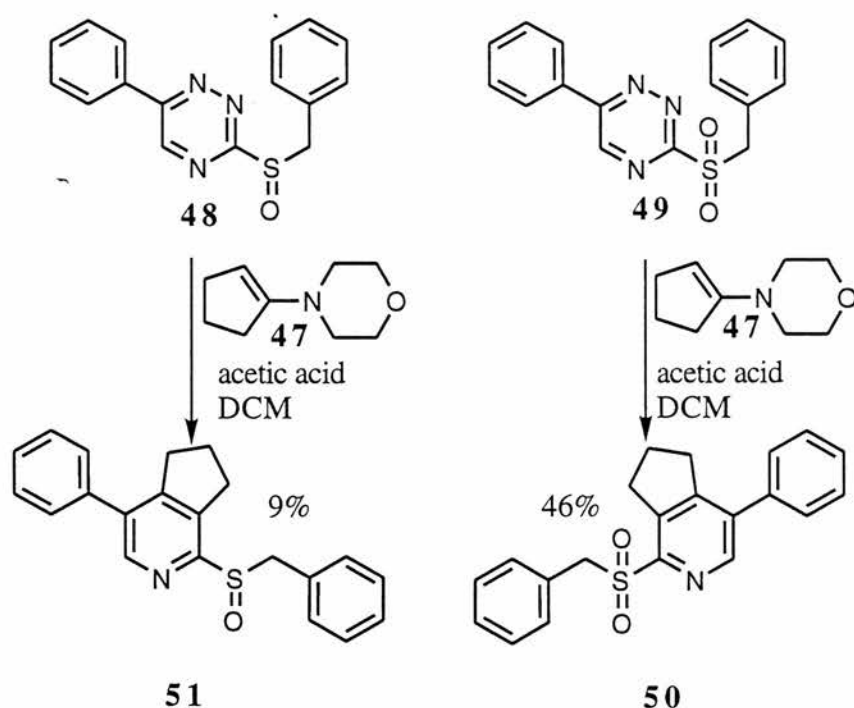
Additional electron-withdrawing groups on the 1,2,4-triazine[46] (C6 or C3/C5/C6) are sufficient to reverse the normal regioselectivity and at the same time increase the rate of participation in the inverse electron demand Diels-Alder reaction.[47,48]

A 1,2,4-triazine **52**, bearing electron-donating substituents, can also undergo a normal Diels-Alder reaction[49] with for example, dimethyl acetylenedicarboxylate **53** to give **54**.
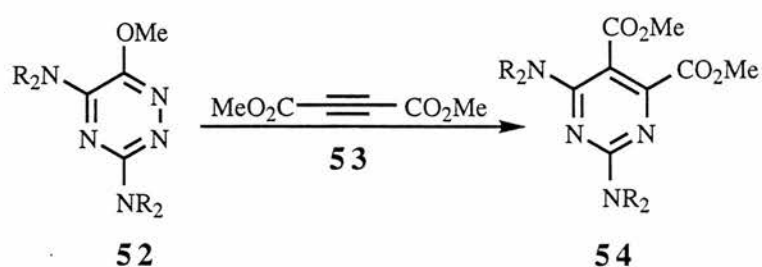
The influence of the dienophile on the reactivity of 1,2,4-triazines[50] in the inverse electron demand Diels-Alder reaction is summarised below. The more electron-rich dienophiles require milder reaction conditions and also give an increased regioselectivity.[46-48,51-53]

DIENOPHILE REACTIVITY

$$X = \underset{}{\boxed{}}N \;>\; O\underset{}{\bigcirc}N \;>\; Me_3SiO \;\geq\; EtS$$

$$R = \; H \quad > \quad Me$$
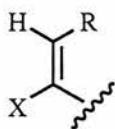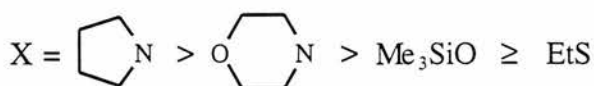
DIENOPHILE REGIOSELECTIVITY

$$X = \underset{}{\boxed{}}N \;>\; Me_3SiO \;>\; O\underset{}{\bigcirc}N$$

$$R = \; H \quad > \quad Me$$

7. <u>Intramolecular Diels-Alder reaction of 1,2,4-triazines</u>

The intramolecular Diels-Alder reaction in contrast[54] to the intermolecular reaction involves the simultaneous formation of two fused rings. The chain which connects diene and dienophile is important in several ways.

- The length of chain which separates diene and dienophile is vital in order that the molecule can adopt a conformation in which the diene and dienophile can achieve the correct alignment for reaction; i.e. a three-atom tether is best whereas a five-atom tether gives no enhancement of reaction rates relative to those found in intermolecular Diels-Alder reactions.

- Groups in the connecting chain which are conformationally restrictive reduce the degrees of freedom in the connecting chain and hence reduce the significance of the entropic component of the activation energy.

A considerable synthetic effort has been put into the synthesis of a variety of 1,2,4-triazines with the dienophile-containing chain attached to C-3, C-5 or C-6.[55,56] For reactions with tethering at C-3, for example **55**, the mode of cycloaddition is across C-3/C-6 and the expulsion of nitrogen from **56** gives fused pyridines **57**.[57]

$$R^1 = R^2 = H, \text{ alkyl, Ar}$$
$$X = S, SO, SO_2, CR_2, O, NR$$
$$n = 1, 2, 3$$
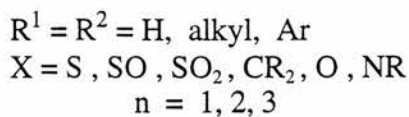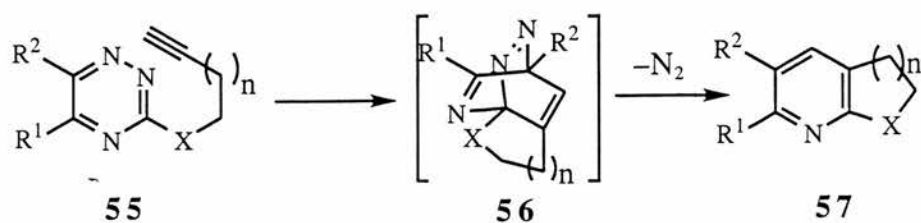
In the above reaction, where X = S and n = 1 i.e. **58**, the Diels-Alder reaction is carried out by heating under reflux in dioxan for 24 hours[58] to form **59**.[59] If instead the sulphide **58** is oxidised to the sulphoxide **60**, cyclisation spontaneously occurs at room temperature.
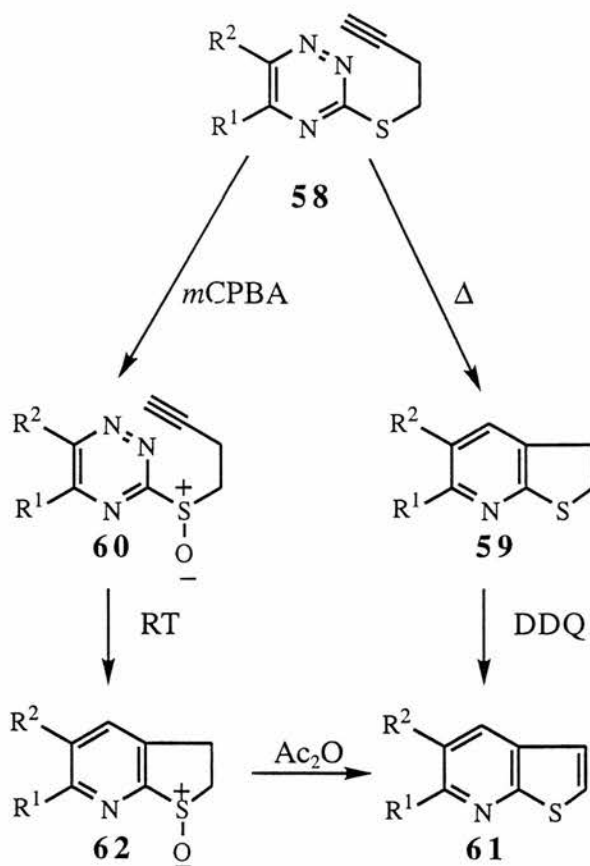
The corresponding sulphone, in contrast, may be cyclised at a significantly slower rate than the sulphoxide, but still at room temperature. Although the sulphone is a more

electron-deficient molecule the observed rates of reaction are in the order sulphoxide >> sulphone > sulphide. This may be explained by looking at the bond angles of dimethyl sulphone, dimethyl sulphoxide and dimethyl sulphide which are 102.6 °, 96.6 ° and 99.2 ° respectively.[54] The smaller the C-S-C bond angle, the closer the diene is to the dienophile. Thieno[2,3-*b*]pyridines **61** can be formed either by dehydration of **62** using acetic anhydride or dehydrogenation of **59** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

The related reactions in the oxygen-linked series have been described by Seitz *et al.*[60] The cycloadditions require heating of the tethered butynyl triazine **63** in either chlorobenzene (b.p. 132°C) or diphenyl ether (b.p. 258°C) to give the fused pyridines **64**, **65** and **66**.
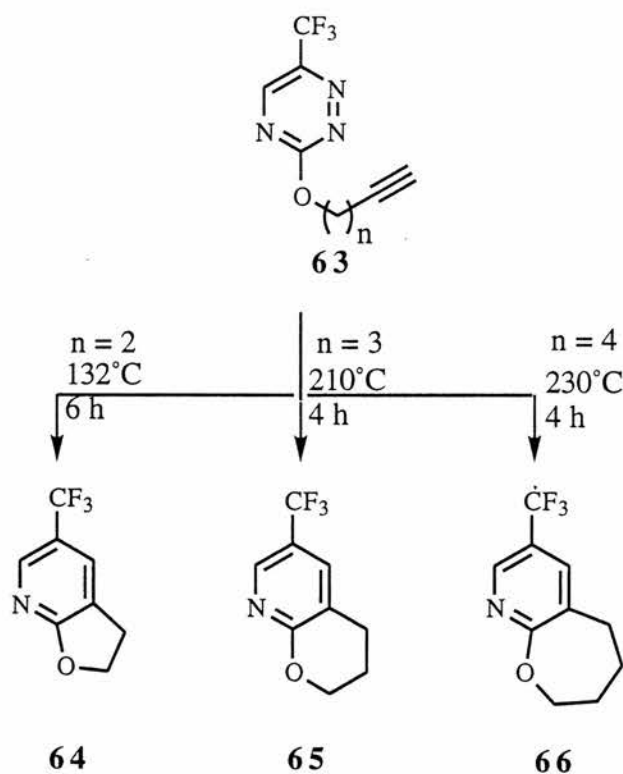
The dienophile may also be tethered through a nitrogen atom.[61] The methanesulphinate group is displaced from **67** by the dienophile **68** to form the substituted aminotriazine **69** which then undergoes a Diels-Alder reaction in boiling bromobenzene for 50 hours to form **70**. The amino group, being electron-donating,

reduces the observed reactivity and extreme conditions are therefore required. The presence of the amino group on the 1,2,4-triazine results in the LUMO of the diene being raised; the frontier-orbital overlap would therefore decrease and the reaction would therefore be more difficult.
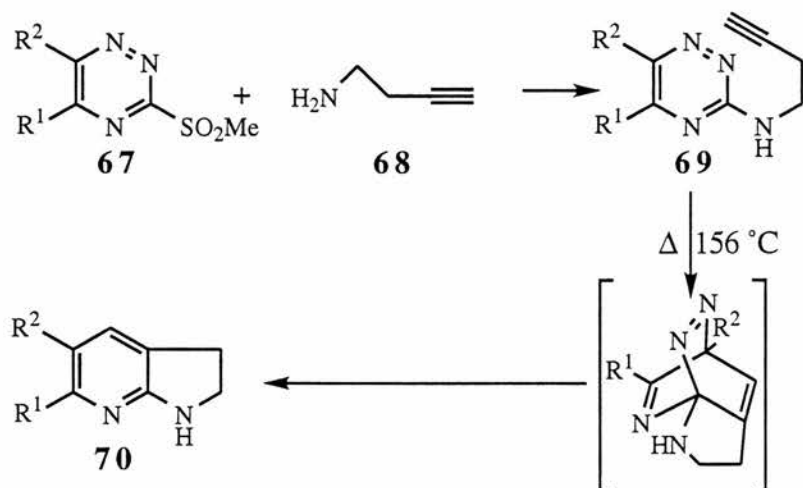
An example in which the tether contains no heteroatom is shown below[62] and results in the synthesis of 2,3-cyclopentenopyridines **71**.[56] **72** is converted to its carbanion and reacted with a 3-methylsulphonyl-1,2,4-triazine **67**. The methanesulphinate group is displaced and cyclisation occurs at room temperature to give the cyclopentenopyridine **71** in almost quantitative yield. 5,6,7,8-Tetrahydroquinolines[63] are synthesised by the corresponding reaction involving a tether containing an additional CH_2 group.
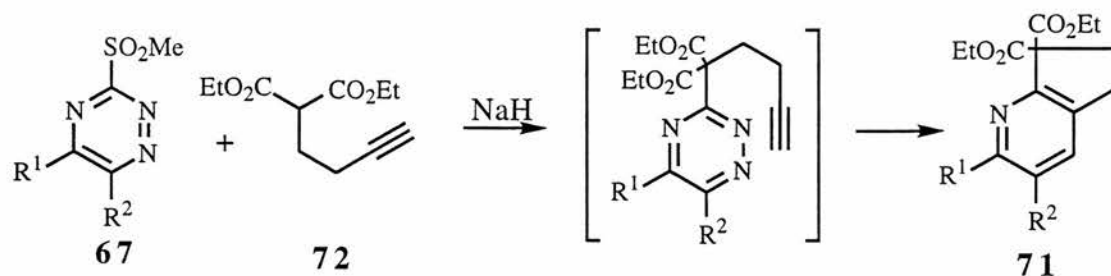
The displacement of methanesulphinate from **67** with *o*-(trimethylsilylethynyl)phenoxide **73** takes place at room temperature, in almost

quantitative yields in many cases, to give benzfuro[2,3-*b*]pyridines **74**.[64] The aromatic ring which is incorporated into the tether increases the rigidity of the latter and enhances the entropic assistance.
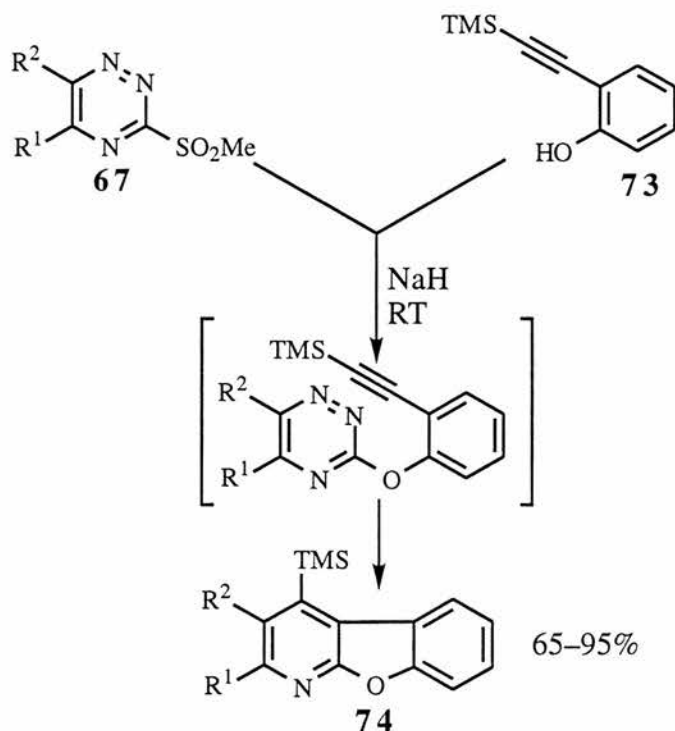
Similarly, a nitrile dienophile[56] in the triazine **75** results in cycloaddition in hot nitrobenzene (140 °C) to give benzfuro[2,3-*b*]pyrazines **76**.[65]
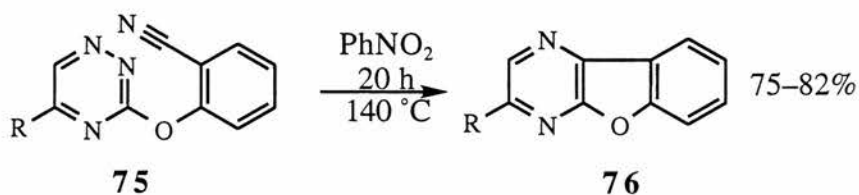
The dienophile may also be tethered to C-6 of the 1,2,4-triazine.[54] In the example below, once again rates of cycloaddition are in the order sulphoxide >> sulphone > sulphide. The sulphide **77** undergoes cycloaddition in low yields in hot nitrobenzene (140°C) to give **78** whereas the sulphoxide **79** undergoes cycloaddition at room temperature to give **80**. Once again, the fully aromatic compound **81** is obtained

by dehydrogenation of **78** or treatment of **80** with acetic anhydride. The mode of cycloaddition is once again across C-3/C-6 with condensed pyridines being produced.
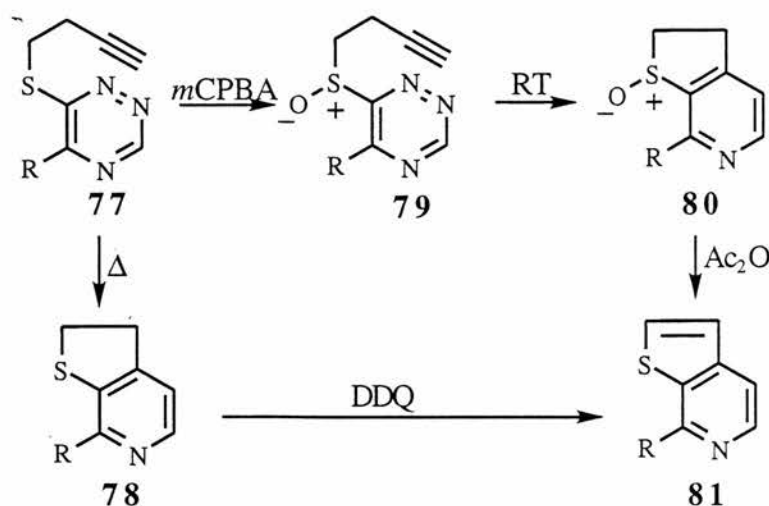
If the dienophile is tethered to C-5 of the 1,2,4-triazine to give **82**, cycloaddition is constrained to occur across the N-2/C-5 positions.[66] The resulting cycloadduct **83** may in principle give condensed pyrimidines **84** (through elimination of R^2CN) or condensed pyridazines **85** (by elimination of R^1CN); since the bridgehead N-N bond is extremely fragile, the former pathway should be, and is shown to be, exclusively observed.

$$X = NH , O , S , CR_2$$
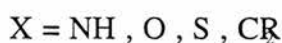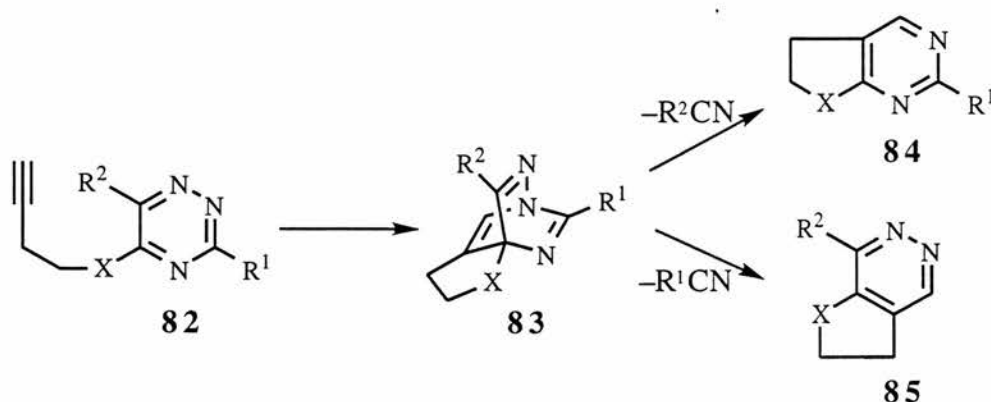
5-(3-Butynyloxy)-1,2,4-triazines **86** may be heated under reflux in 1,3,5-

triisopropylbenzene (TIPB, b.p. 235°C) for 2–3 days to give dihydrofuro [2,3-*d*] pyrimidines **87** in low yields. When the sidechain of the dienophile carries an additional ethyl substituent as in **88** and the reaction mixture is heated in TIPB for 2 days a 38% yield of 2-ethyl-6-(methylthio)-2,3-dihydrofuro[2,3-*d*]pyrimidine **89**[67] is obtained. Such an increase in reaction rate is presumably, once again, due to an "entropic assistance" provided by the ethyl substituent which makes it easier for the (1-ethyl-3-butynyl)oxy side chain to orientate itself into the conformation preferred for cycloaddition to take place.

88

TIPB
2–3days
Δ

89

R^1 = SMe
38%

86

TIPB
2days
Δ

87

R^1 = SMe
trace–10%
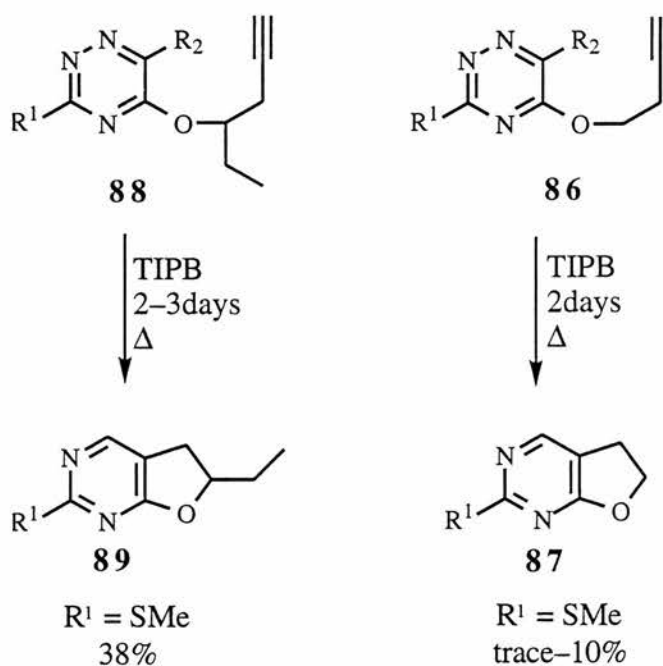
By analysis of relative reaction rate and yields one can conclude that reactivity is influenced by the connecting group in the order $SO > SO_2 > S > O > N$.

Our current efforts in the group have been directed to the extension of such inverse electron demand Diels-Alder reactions to the synthesis of polymers. Bis-1,2,4-triazines are therefore attractive synthetic targets for use as bis-dienes. Relatively little is known about such compounds, although several sporadic reports of the synthesis of such compounds have appeared in the literature. The following section describes the various syntheses described.

8. 3,3'-Linked bis-1,2,4-triazines

3,3'-Bitriazinyls

In 1936, Dedichen reported the synthesis of 3,3'-bitriazinyls **90**[68] from the reaction of oxalamidrazone **91**[69] (prepared by passing dicyanogen over hydrazine hydrate) with various glyoxals **92**.
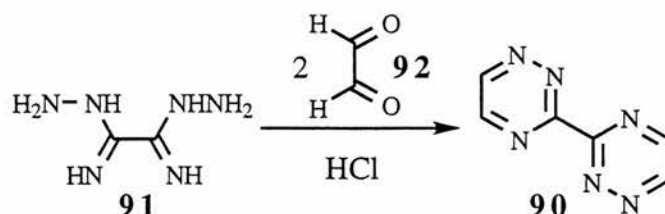
An improved synthesis of oxalamidrazone **91** by the reaction of 95% hydrazine on dithiooxamide **93**[70] and the subsequent reaction with diketones such as, for example, 2,2'-pyridil **94** resulted in the formation of 5,5',6,6'-tetrakis(2-pyridyl)-3,3'-bi-(1,2,4-triazinyl) **95**.
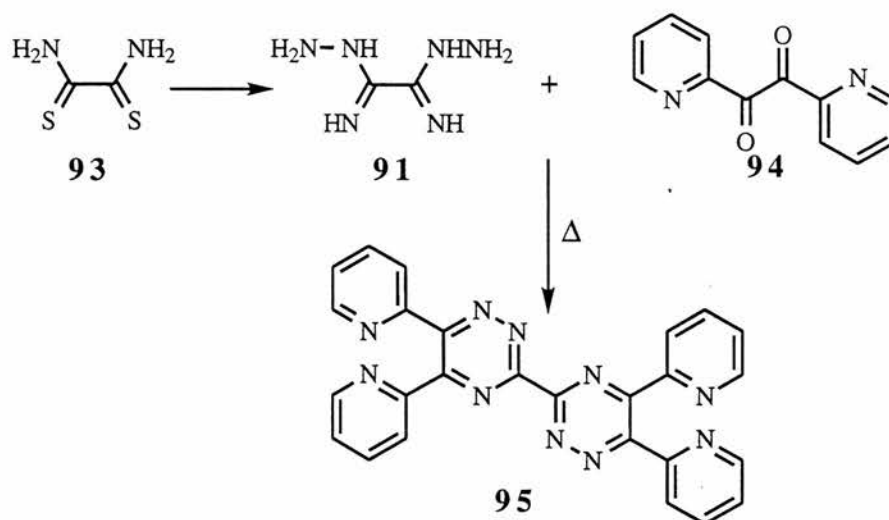
Following on from this work, Culbertson and Parr reported the reactions of amidrazones and bis-amidrazones with glyoxals (Ar-COCHO) and bis-glyoxals [Ar'(COCHO)₂] to form 3,5-disubstituted 1,2,4-triazines, 5,5'-disubstituted 3,3'-bi-

1,2,4-triazinyls and 3,3'-disubstituted 5,5'-bi-1,2,4-triazinyls, the only limitation of the reaction being the availability of the required amidrazones and glyoxals.[71] The example shown below describes the reaction of oxalamidrazone **91** and phenylglyoxal **96**, *p*-hydroxy- **97** and *p*-nitro- phenylglyoxal **98** to give 5,5'-bis-(phenyl)-3,3'-bi-1,2,4-triazinyl **99**,[72] 5,5'-bis-(*p*-hydroxyphenyl)-3,3'-bi-1,2,4-triazinyl **100** and 5,5'-bis-(*p*-nitrophenyl)-3,3'-bi-1,2,4-triazinyl **101** respectively.
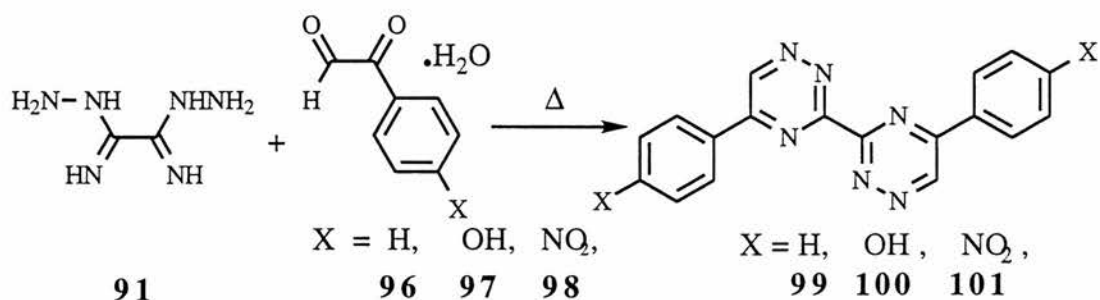
3,3'-Linked bis 1,2,4-triazines

A CIBA patent[73] described the synthesis of stilbenes **102** as fluorescent whitening agents for incorporation in polyester fibres by the oxidative coupling of the corresponding *p*-tolyl heterocyclic compounds in potassium hydroxide/dimethylformamide where the oxidising agent was dry air (1–3 litres per hour).

102
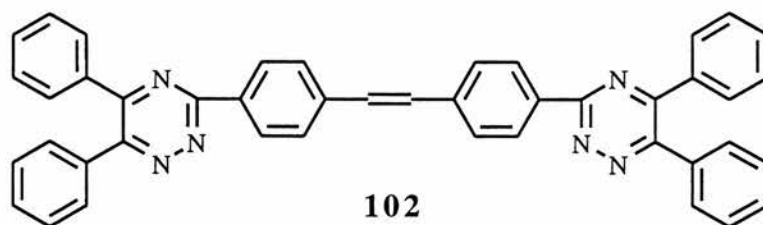
The reaction of terephthaloyldiamidrazone **103**[74] with the diketone **104** gave the bis-triazine **105**,[75] the diketone **104** being prepared from 2-(phenylacetyl)quinoxaline by selenium dioxide oxidation.
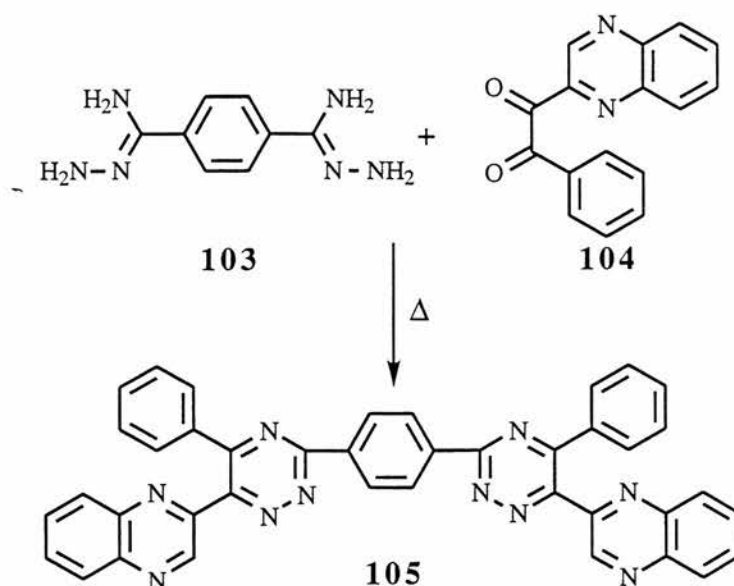
Metze and Kort described[76] the synthesis of 3,3'-linked-bis-1,2,4-triazines **106** by the reaction of diacetyl **107** and dihydrazides **108** in the presence of ammonia to give **106** (where n = 2,3,4,5,8 or 14).
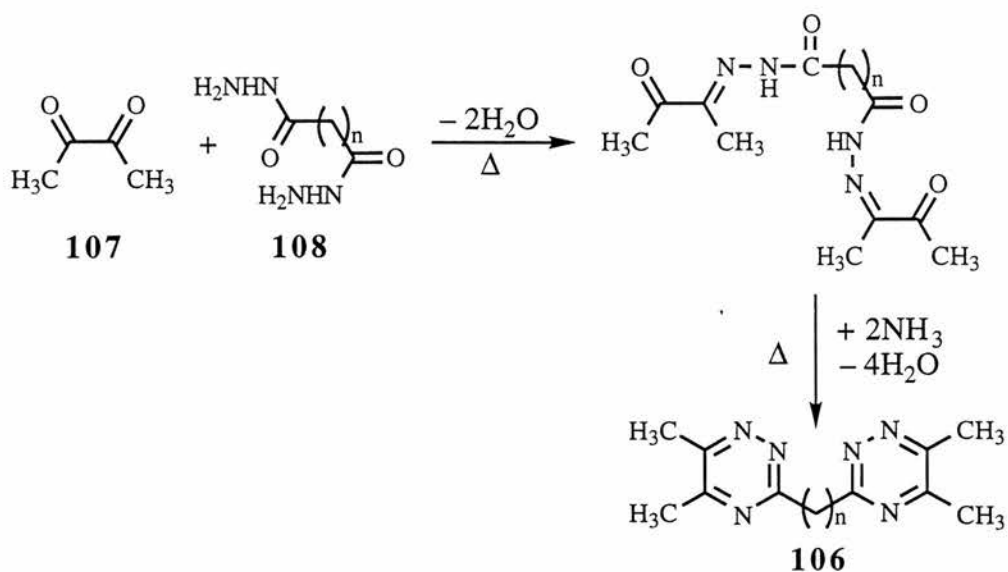
3,3'- Disulphide linked bis-1,2,4-triazines

Tisler reported[77] the synthesis of bis(5-phenyl-1,2,4-triazin-3-yl) disulphide **109** by the reaction sequence shown below. The reaction of phenylglyoxal **96** with thiosemicarbazide **110** gave the intermediate monothiosemicarbazone **111** which was

cyclised to give the 1,2,4-triazine-3-thione **112**. The titration of the 3-thione with an aqueous solution of iodine in potassium iodide gave the 3,3'-disulphide-linked bis-1,2,4-triazine **109** in good yield.
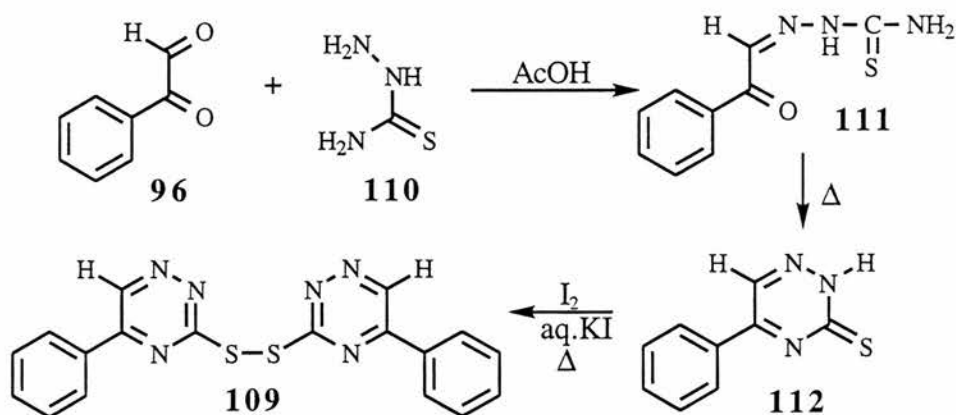
In 1952, Gianturco described[78] the synthesis of bis(5,6-diphenyl-1,2,4-triazin-3-yl) disulphide **113** by a similar reaction starting from **114**.[79]
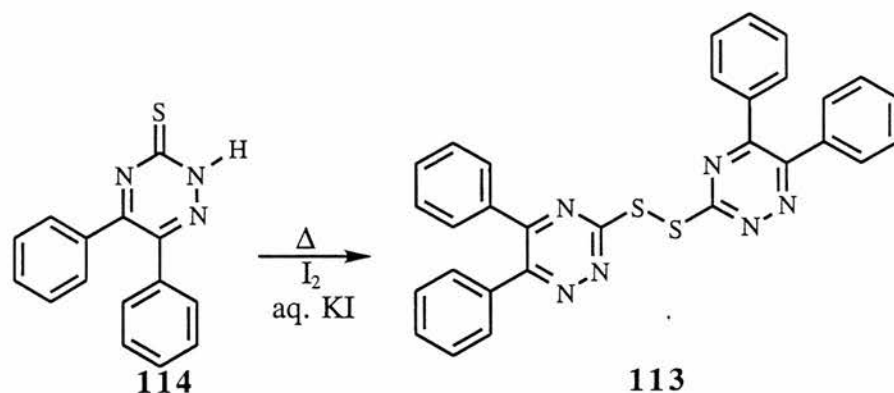
9. **5,5'-Linked bis-1,2,4-triazines**

5,5'-Bitriazinyls

Coupling of a 5-unsubstituted 3-(methylthio)-1,2,4-triazine **115**[80] to give the 5,5'-linked bitriazinyls **116** and **117** is brought about by the action of potassium cyanide in dioxan[81] or sodium in methanol.[82] In the former reaction, a high yield of compound **116** is obtained; however, since a 5 molar excess of potassium cyanide is apparently required for the reaction, the reaction is not suitable for large scale preparations on safety

grounds. In the latter case nucleophilic substitution of the methylthio group by methoxide results in the formation of the methoxy dimer **117** and only a trace of the methylthio dimer **116**.
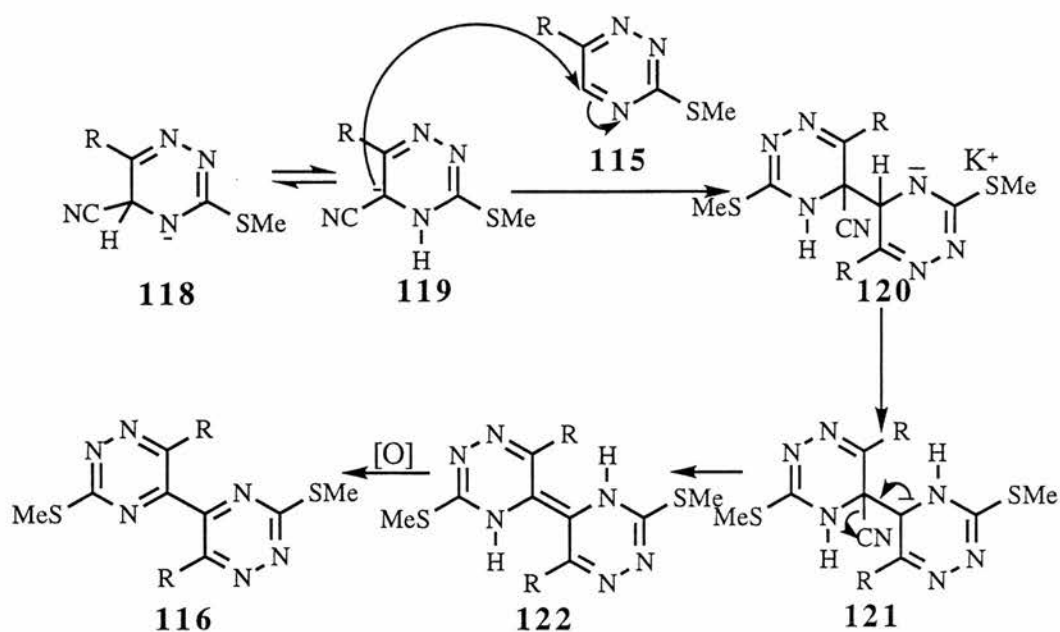
In the potassium cyanide reaction the intermediate **118** is postulated to form an anion **119**. A possible mechanism has been postulated below.
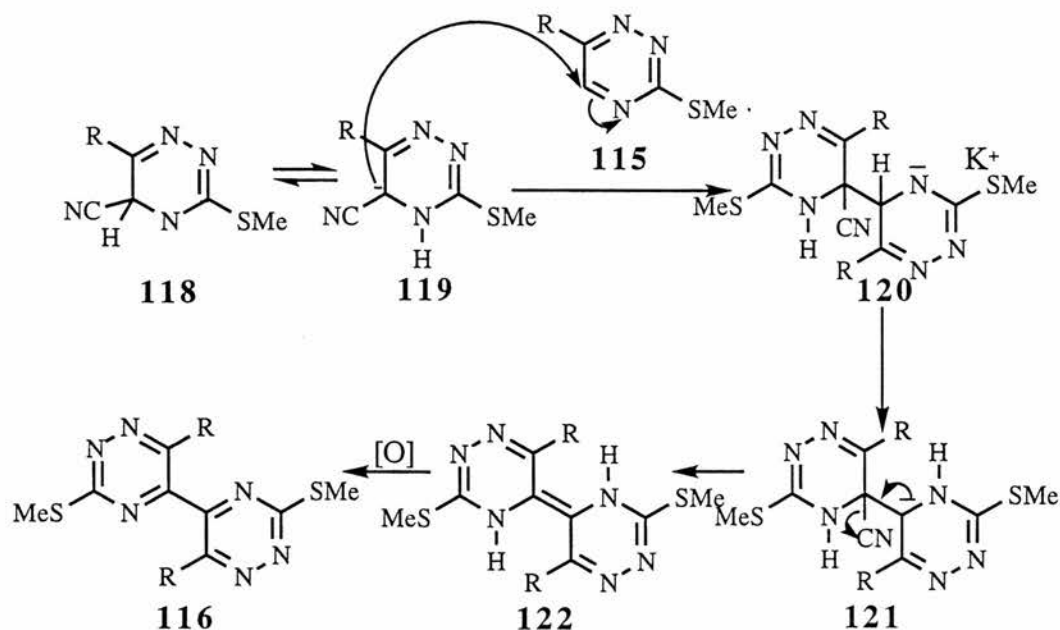
The anion **119** then presumably attacks a second molecule of **115** to give the anion **120**, which in turn rearranges to give **121**; elimination of cyanide ion then gives **122** which finally undergoes oxidation to the bitriazinyl **116**. The mechanism shown is postulated, however no detailed mechanistic study has been carried out.

The sodium in methanol (dissolving metal) reaction on the other hand presumably involves one-electron reduction of the triazine ring, dimerisation of the radical anion **123** and again a final oxidation step to give the methoxy dimer **117**.

123
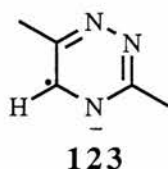
5,5'-Linked bis-1,2,4-triazines

5,5'-(1,4-Phenylene)bis-[3-(2-pyridyl)][1,2,4-triazine] **124** was prepared by Culbertson[83] by the reaction of 1,4-phenylenebisglyoxal dihydrate **125** and 2-pyridylhydrazidine **126**.
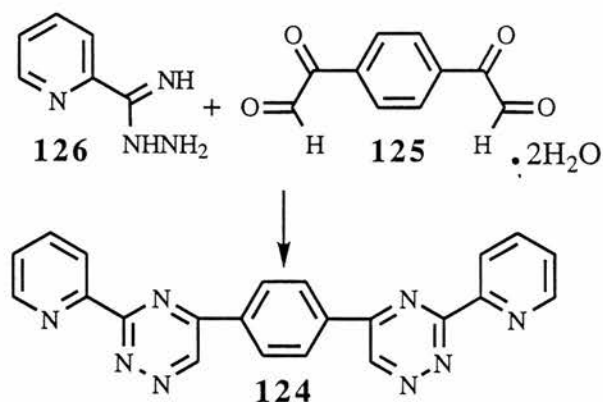
5,5'-Disulphide linked bis-1,2,4-triazines

Li and Wang described[84] the substitution reaction of N-[(6-methyl-3-methylthio-1,2,4-triazin-5-yl)]pyridinium chloride **127** with hydrogen sulphide in pyridine at room temperature to give 6-methyl-3-methylthio-1,2,4-triazine-5-thione **128**. Compound **128**

reacted with a further molecule of the pyridinium salt **127** in aqueous pyridine at room temperature, to form bis-(6-methyl-3-methylthio-1,2,4-triazin-5-yl) sulphide **129**.
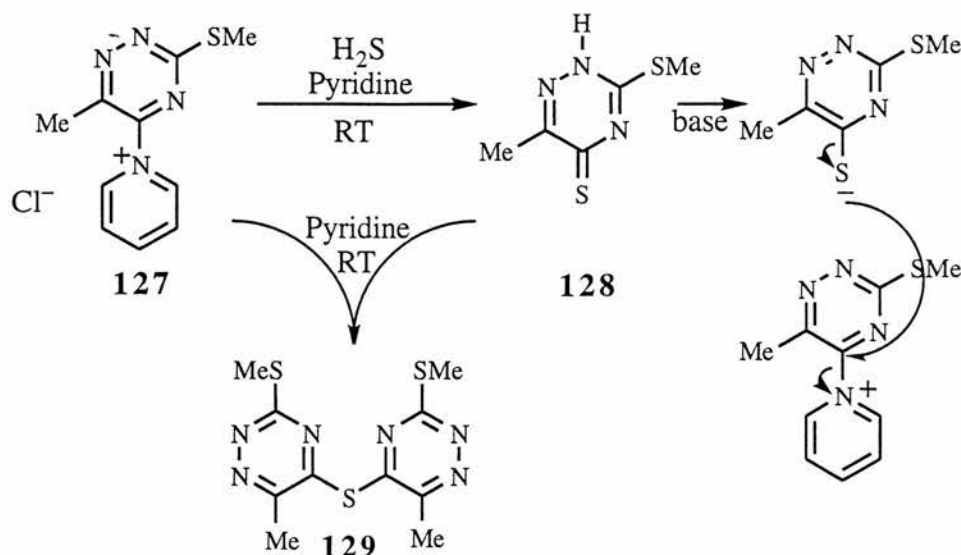
For our purposes the 5,5'-linked bis-1,2,4-triazines are more attractive than 3,3'-linked analogues both for steric reasons (since a Diels-Alder reaction occurring across C-3 and C-6 might be subject to steric hindrance in the latter) and also because the resulting polymer produced may contain at least a proportion of linear 2,5-disubstituted pyridine units. The sporadic reports of bis-triazine synthesis discussed have not been of a general nature and therefore, in order to derive a more general synthetic route to bis-1,2,4-triazines, it was necessary to look first at the synthetic routes which are available for mono-1,2,4-triazines.

10. **Mono 1,2,4-triazine synthesis**

The preparation of 1,2,4-triazines has found widespread interest in the literature and has been reviewed.[85] The parent compound **130** was first prepared by Paudler and Barton[86] in 1966 by the reaction scheme shown below, involving reaction of glyoxal **92** and the diamino ester **131**. The ester **132** was hydrolysed and finally decarboxylated to the acid **133**.
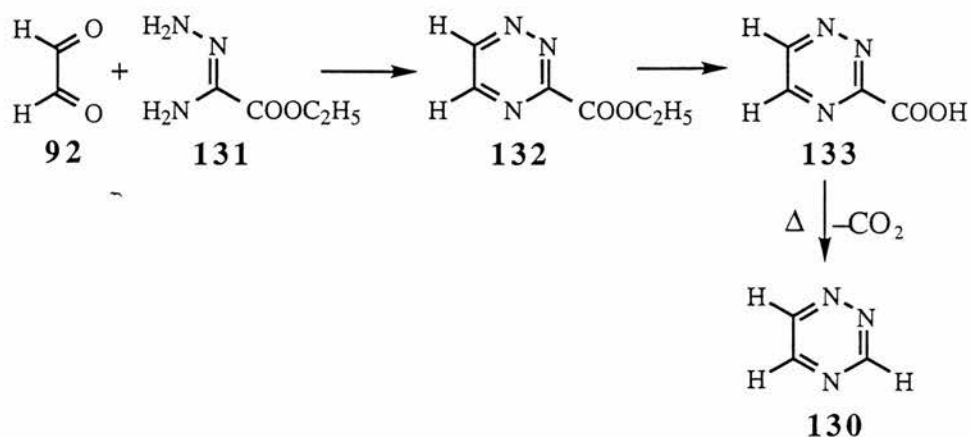
A variety of methods have been established for the synthesis of 1,2,4-triazines without a functional group directly bonded to the 1,2,4-triazine ring.

The reaction of the amidrazone **134**[70] with a 1,2-dicarbonyl compound **135**[87,88] results in the formation of the intermediate **136**. The ring closure is normally carried out in the same reaction pot using base to give the 1,2,4-triazine **137**. The reaction is normally carried out by the addition of the 1,2-dicarbonyl compound to the free amidrazone or to an amidrazonium salt in the presence of one molar equivalent of base. Since the first step of the reaction i.e. condensation of the hydrazono group with the carbonyl group is fast, whereas the second step i.e. condensation of the amide group with the other carbonyl group is slow, it is often possible to isolate the intermediate if required.
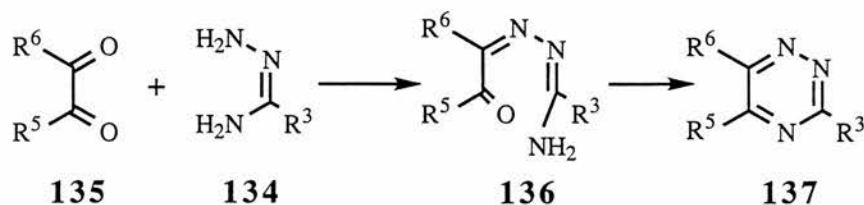
If instead the reaction is carried out in the presence of acid, bis-(amidrazones) **138** are formed and can be transformed by acidic hydrolysis into the corresponding 1,2,4-triazine **139**. 6-Substituted 1,2,4-triazines **139** are formed almost exclusively, rather than the 5-substituted compound **140**, when the glyoxal is monosubstituted.[89]
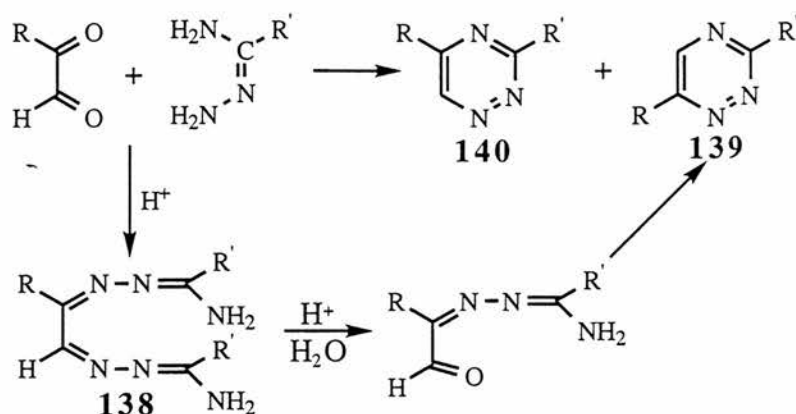
As an alternative to amidrazones, semicarbazide **141**, thiosemicarbazide **110**, selenosemicarbazide **142**, or aminoguanidines **143** give 1,2,4-triazin-3-ones **144**,[90] 1,2,4-triazine-3-thiones **145**,[90] 1,2,4-triazine-3-selenones **146**[91] and 3-amino-1,2,4-triazines **147**[92] respectively. Whereas semicarbazide itself tends to give only acyclic semicarbazones which require to be cyclised in a separate step,[93] *S*-methylthiosemicarbazide **148** reacts with a 1,2-dicarbonyl compound in the presence of base to give the 3-methylthio-1,2,4-triazine **149** directly.[94]
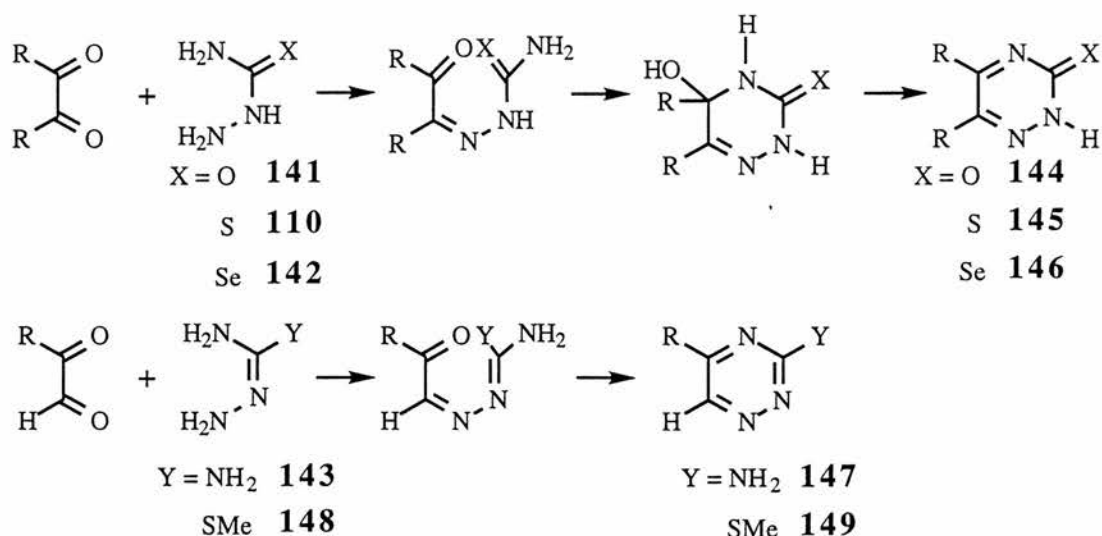
The reactions of semicarbazide and thiosemicarbazide with monosubstituted glyoxals give 5-substituted triazines.[85] The reactions of semicarbazide **141** and thiosemicarbazide **110** with monoximes of 1,2-dicarbonyl compounds **150** however are

of particular interest for the synthesis of 6-substituted-1,2,4-triazine derivatives **151**.
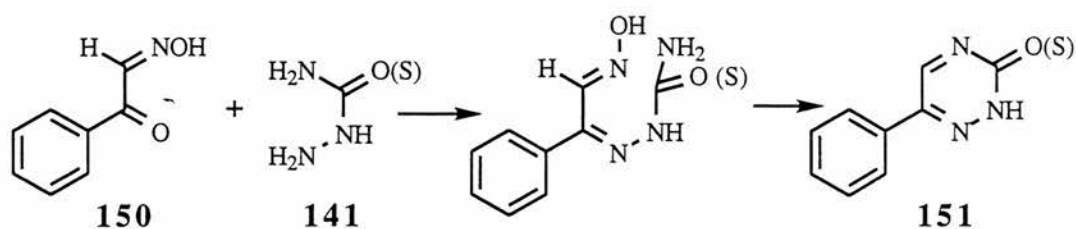
An unusual method for synthesis of 1,2,4-triazines involves the reaction of 1,2,4,5-tetrazines **152** in inverse electron demand Diels-Alder reactions. Cycloaddition with imidates **153**[95] affords 1,2,4-triazines **154** via the bicyclic intermediate **155** and the dihydro-1,2,4-triazine **156**. The reaction of tetrazines **152** with cyanamides **157**[96] via the bicyclic intermediate **158** gives the 5-amino-1,2,4-triazine **159**; or aliphatic aldehyde dimethylhydrazones **160**[97] in which the elimination of nitrogen from the adducts **161** affords 4-aminodihydro-1,2,4-triazine **162** were also successful.
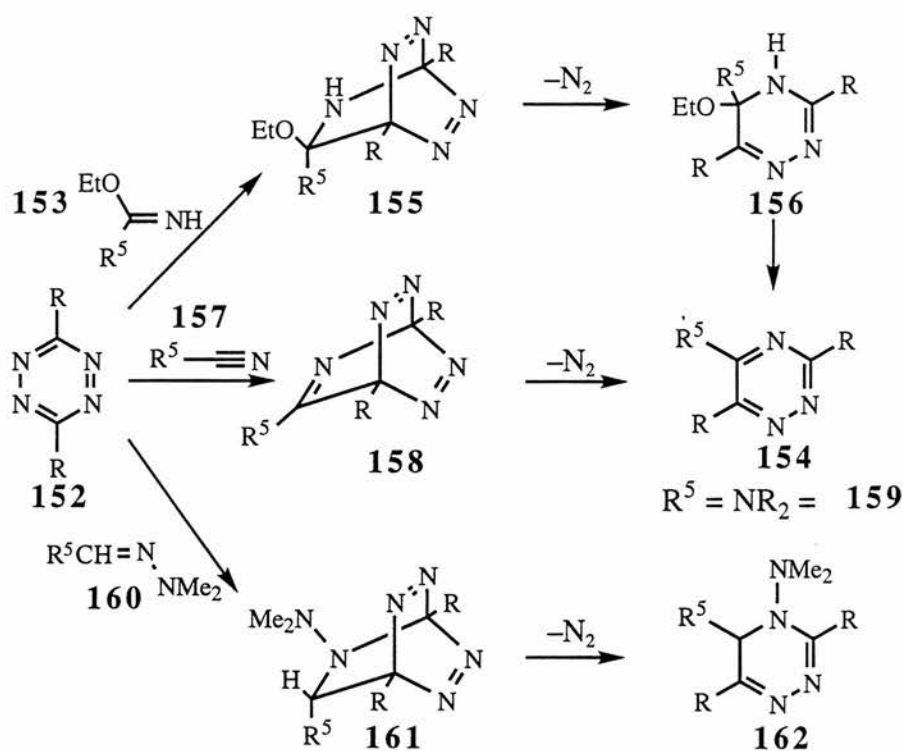
A variety of synthetic routes to mono-1,2,4-triazines are therefore available, however for the purpose of this research project a route to electron-deficient 5,5'-linked bis-1,2,4-triazines was sought. The bis-triazines are attractive synthetic targets for potential use as bis-dienes. Chapter 2 (Discussion) describes the novel syntheses which have been developed to these compounds.

Chapter 2
Discussion

11. Bis-1,2,4-triazines as monomers in the inverse electron demand Diels-Alder reaction

As has been discussed in the Introduction 1,2,4-triazines are extremely electron-deficient dienes and take part in the inverse electron demand Diels-Alder reaction with various electron-rich dienophiles. It can be inferred that the inverse electron demand Diels-Alder reaction of bis-1,2,4-triazines with bis-dienophiles might similarly occur to give polymers. Since bis-1,2,4-triazines are to be used as monomers in the Diels-Alder reaction, 3,3'-linked bis-1,2,4-triazines **163** are not attractive as, even if the linker group which separates the two triazine rings is such that the triazine rings are spatially discrete, the reaction of the triazine rings with dienophiles might be hindered sterically. Cycloaddition across N-2/C-5 may result in nitrile elimination and chain cleavage and therefore the preferred mode of cycloaddition is across C-3/C-6 with the thermodynamically driven loss of molecular nitrogen giving substituted pyridines. Sterically, at least, this mode of cycloaddition is more likely when the triazines are linked through C-5 and it was thus decided to concentrate efforts on this type of bis-1,2,4-triazine **164**. The polymer produced from these 5,5'-linked systems may possess the added advantage of at least a proportion of linear 2,5-disubstituted pyridine units, which ought to offer the best chance of a polymer with a high T_g.
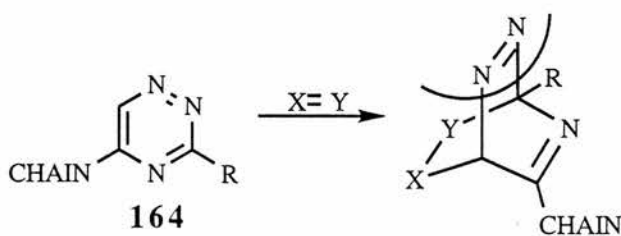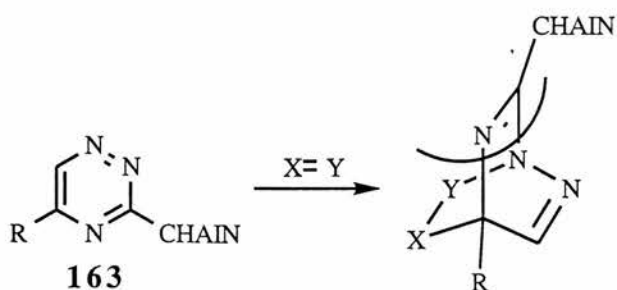
Since no general method was available for the synthesis of suitable 5,5'-linked bis-1,2,4-triazines, this research project has involved the development of routes for the synthesis of these compounds.

12. <u>**Bis diene synthesis: 5,5'-Bis-1,2,4-triazines**</u>

Two methods for formation of such bis-1,2,4-triazine monomers have been investigated in parallel.

- **Building a triazine ring at either 'end' of a core unit**
- **Coupling reactions of preformed mono-triazines to each other or to a central core unit**

In the former case the bis-1,2,4-triazine is formed from the reaction of a bis-1,2-dicarbonyl compound and a semicarbazide derivative to give the triazine directly. In the latter case, mono-triazine coupling reactions can be achieved in two ways; firstly one can react two differently functionalised triazines together, and secondly, one can use a substitution reaction to attach a triazine unit to the 'ends' of a central core unit.

Construction of 1,2,4-triazine at either 'end' of a core unit

As discussed elsewhere (page 29) 1,2,4-triazines are most often prepared by reaction of 1,2-dicarbonyl compounds with semicarbazide derivatives, giving acyclic semicarbazones which require to be cyclised in a separate step.[93] If instead, *S*-methylthiosemicarbazide is used,[98] the 3-methylsulphanyl-1,2,4-triazine is formed directly.[80] Therefore the synthesis of a bis-1,2,4-triazine can be achieved in principle by the reaction of a bis-glyoxal **165** with *S*-methylthiosemicarbazide **148**; the bis-triazines **166** may be subsequently oxidised to their corresponding methylsulphonyl **167** and methylsulphinyl analogues **168**. The reaction scheme used for the synthesis of these compounds is shown below: the diacetyl aromatic compounds **169** are attractive precursors of the required bis-glyoxals since they are readily obtained by Friedel-Crafts acetylation of **170** (unless X is an electron-withdrawing group).
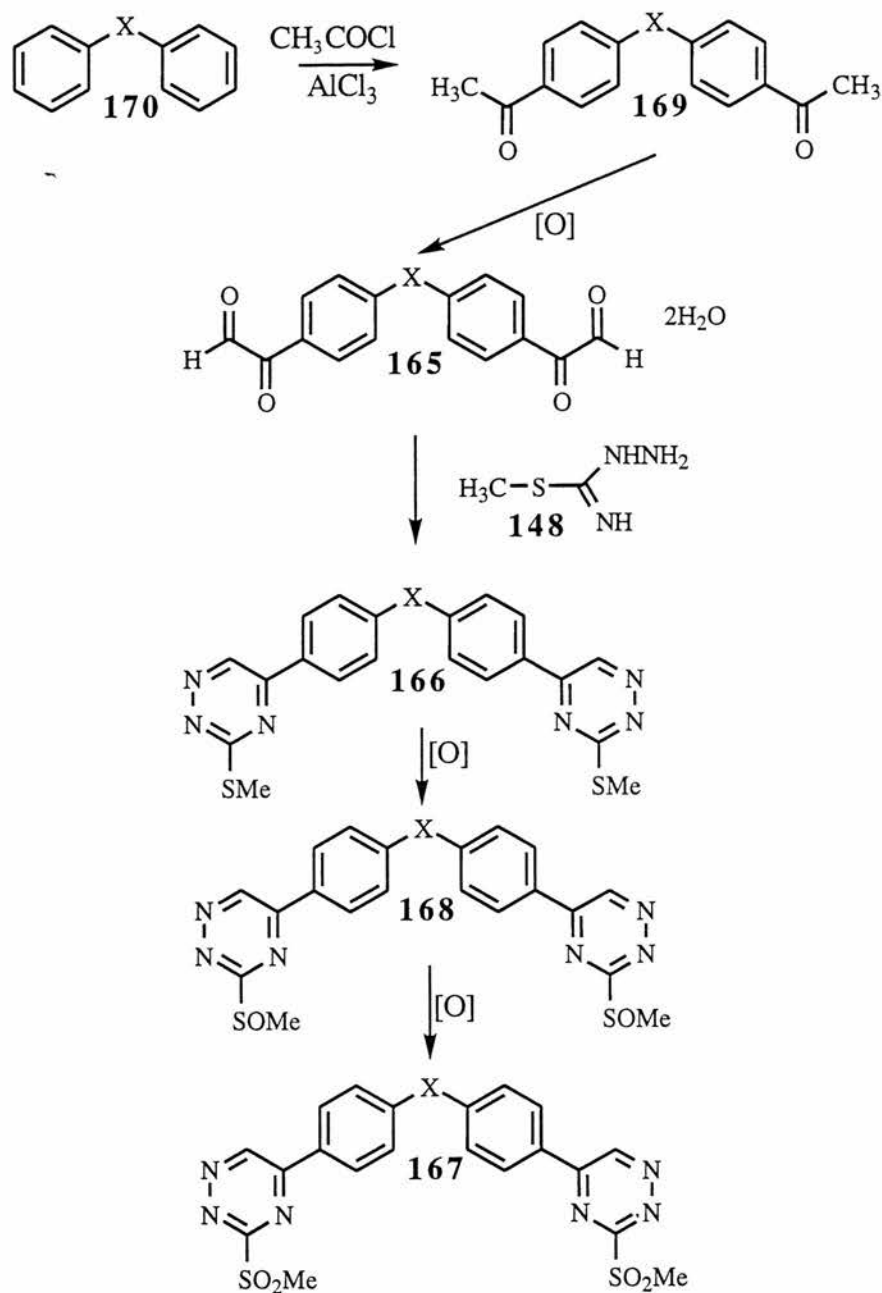
The synthesis of bis-1,2-dicarbonyl compounds was therefore the first synthetic target. Several methods are well known for the synthesis of mono-1,2-dicarbonyl compounds; it must however be stressed that methods for the formation of mono 1,2-dicarbonyl compounds cannot necessarily be applied to the synthesis of bis-1,2-dicarbonyl compounds.

1,2-Dicarbonyl compounds

The formation of benzoins **171** from benzaldehydes **172** and cyanide ion, and their subsequent oxidation (using for example concentrated nitric acid[99]) to afford benzils **173**, constitutes one of the best-known methods for the synthesis of aromatic 1,2-diketones. Problems of mixtures of α-hydroxy ketones are encountered when an unsymmetrically substituted benzoin is required.
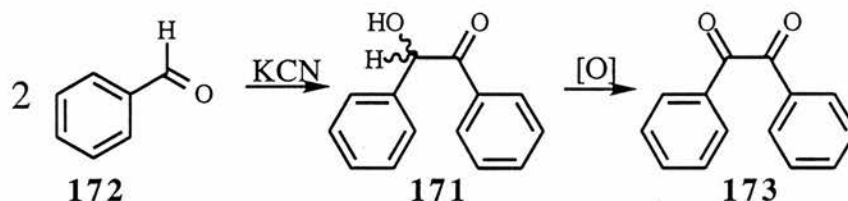
A proposed mechanism for the benzoin condensation reaction is shown below.[100]
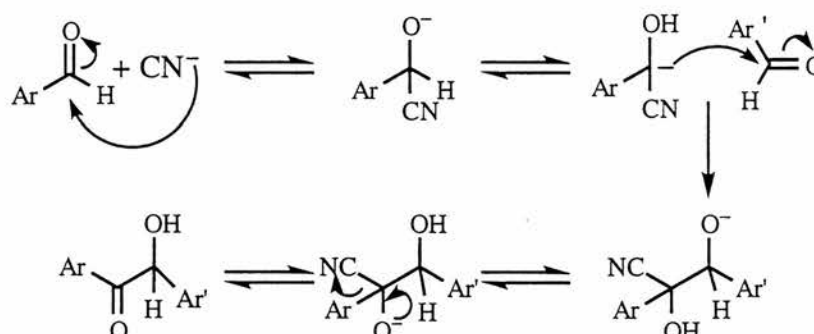
The reaction is reversible and the key step, the loss of the aldehydic proton, can take place because the acidity of the C-H bond is increased by the electron-withdrawing influence of the cyanide group. Therefore, CN⁻ is an extremely effective catalyst for the reaction due to the following factors: it acts as a nucleophile; its electron-withdrawing effect permits loss of the aldehydic proton; and finally it acts as an excellent leaving group.

Bisbenzoins are not an attractive synthetic target, due to the fact that one would need to use a dialdehyde and two molecules of monoaldehyde which would result in mixtures of various α-hydroxy ketones.

The other well-documented method available for 1,2-dicarbonyl compound formation involves the use of selenium dioxide[101] for the oxidation of CH_2CO groups and has been used for the synthesis of bis-1,2-diketones such as p,p'-oxydibenzil **174** from **175**[9,102] and bis-glyoxals such as m- **176**[103] and p- **177**[104]phenylenebisglyoxals from **178** and **179**[87] respectively.

175   SeO$_2$ **174**

m- **178**   **176** m-C$_6$H$_4$

p- **179**   **177** p-C$_6$H$_4$
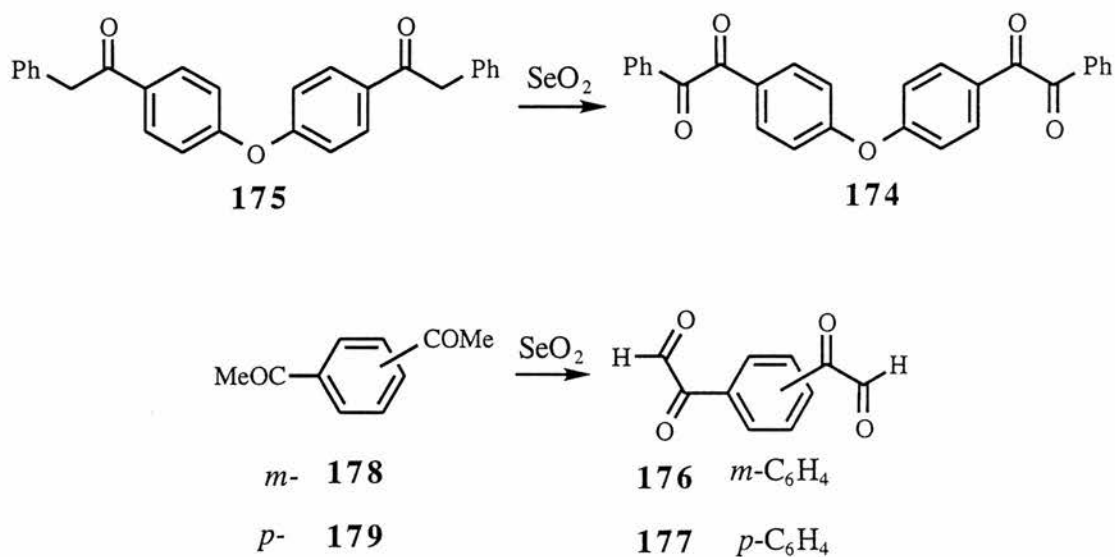
As selenium (which is obtained as the co-product) and its compounds are very toxic and the removal of elemental selenium from the product is extremely difficult, this reaction is not practical for the synthesis of bis-1,2-dicarbonyl compounds, at least on a large scale where purification by column chromatography would prove impracticable. Several mechanisms have been proposed for selenium dioxide oxidations: the first route shown (route 1) involves a selenate ester of the enol[105] whereas in the other (route 2) the principal intermediate is a β-ketoseleninic acid.[106] Other members of this research group have already investigated the formation of bis-1,2-dicarbonyl compounds using selenium dioxide, and although the required compounds were formed, purification proved difficult as selenium precipitated from the reaction mixture over a period of a few days and this route to tetracarbonyl compounds was thus abandoned.
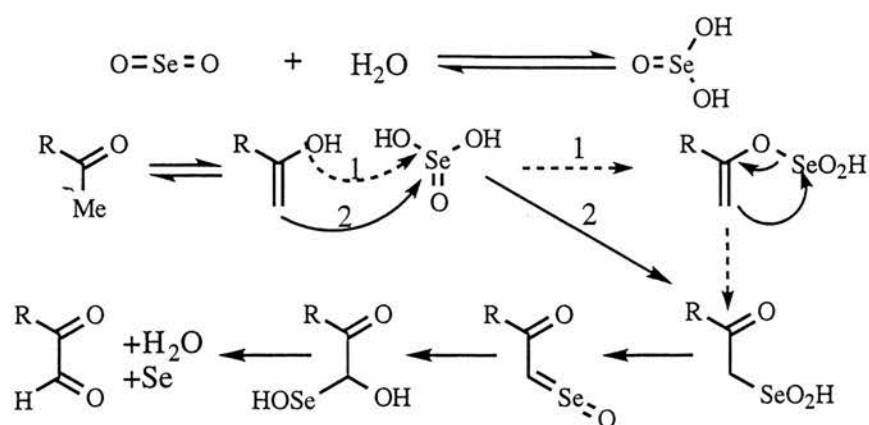
The oxidation of benzylic halides to carbonyl compounds in dimethyl sulphoxide in the presence of silver fluoroborate and base is known.[107] Such methods are unsuitable for the conversion of vicinal dibromides to 1,2-diketones since the latter are unstable in the presence of base and undergo, for example, a benzilic acid rearrangement to give the salts of α-hydroxy acids.[108]

An alternative method for the oxidation of 1,2-dibromo compounds[109] involved the use of substituted stilbenes.[110] Some stilbenes **180** are oxidised to benzils **181** in solutions of hydrobromic acid and hydrogen peroxide in dimethyl sulphoxide.[111] Hydrogen peroxide is not entirely necessary for the reaction, as it is known[112] that dimethyl sulphoxide itself can perform the same task.[113]
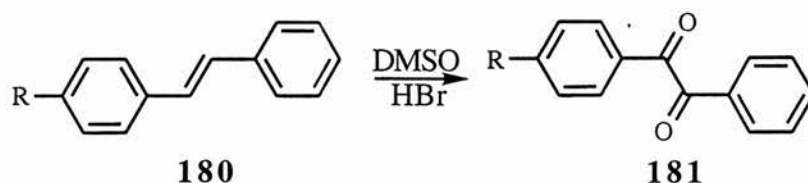
Iodine in dimethyl sulphoxide[114] is a convenient reagent for the conversion of stilbenes and 1,2-diarylethynes **182** to 1,2-diketones **183**. This method has several advantages (for example, increased yields) compared to existing methods which used selenium dioxide (with a small quantity of sulphuric acid) or neutral potassium permanganate.
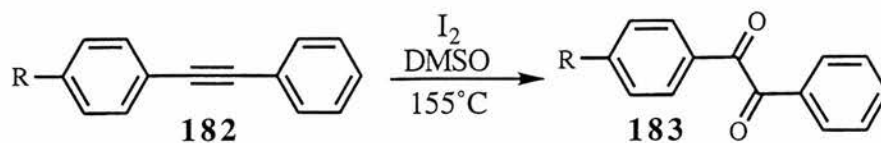
Furthermore it was discovered that stilbene **184** is readily oxidised to benzil **185** by addition of bromine and sulphuric acid in refluxing acetic acid.[115] The intermediate product was shown to be a mixture of meso- and ±-1,2-dibromo-1,2-diphenylethane **186** in the ratio 3:1.
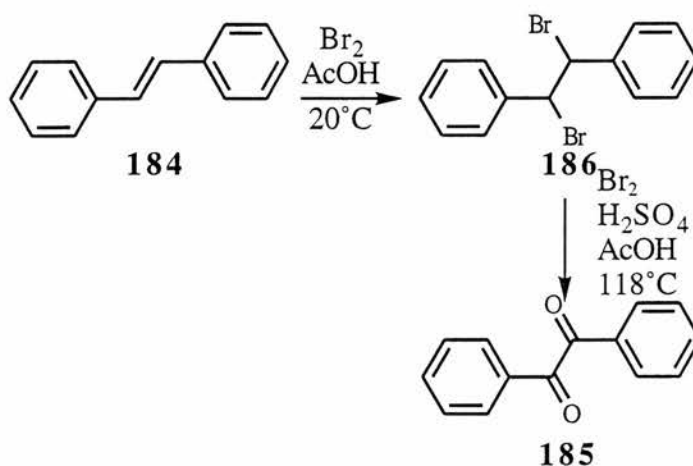
The oxidation of α-bromoketones **187** to 1,2-diketones may also be achieved by the action of dimethyl sulphoxide.[116] Initial bromination of acetylbenzenes **188** and their subsequent reaction with dimethyl sulphoxide forms the required arylglyoxals **189**.
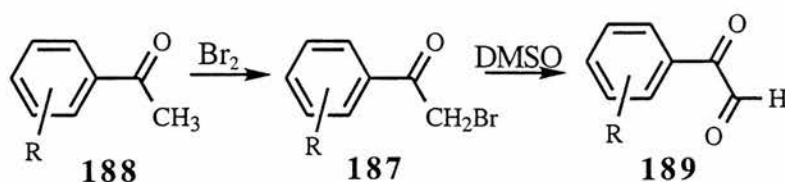
The mechanism postulated in our group for glyoxal formation is shown below. The formation of bromine by the reaction of hydrobromic acid and dimethyl sulphoxide demonstrates the key step required for reaction to occur.

$$2HBr + Me_2SO \rightleftharpoons Br_2 + H_2O + Me_2S$$
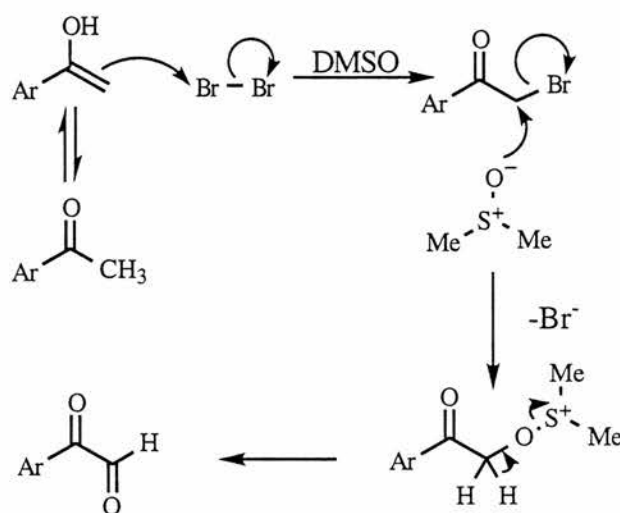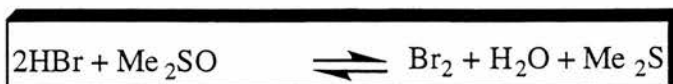
A report of the synthesis of arylenebis-glyoxals by Saikachi and Muto[117] made use of the aforementioned method and described the synthesis of a wide variety of bis-glyoxals.

Bis glyoxal synthesis

Another member of the research group showed that the method of Saikachi and Muto is successful for the oxidation of bis-[p-(2-bromo-2-phenylacetyl)phenyl] ether) aromatic compounds **190** using dimethyl sulphoxide to the corresponding bis-benzil **191**.

190

X = O, bond

191

X = O, bond
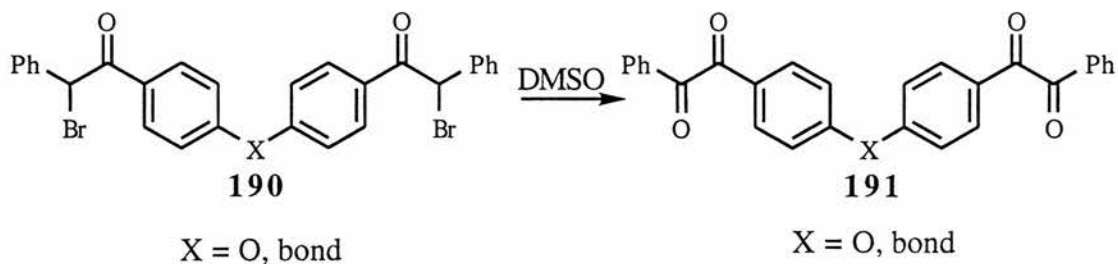
It fails, however, to oxidise the bis-(bromoacetyl)-aromatics **192** cleanly to the bis-glyoxals **165**, large amounts of unreacted dibromo-compound being recovered.
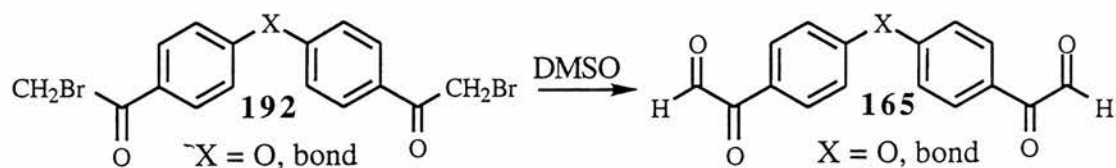
Attempts at oxidation using pyridine N-oxide[118] or triethylamine N-oxide[119] were carried out and unfortunately resulted in the formation of high melting materials which remain unidentified. It is possible that these unwanted products may result from over-oxidation or from a condensation of the bis-glyoxals with the starting compounds. It is also possible that these products may be bis-mandelic acids **193** as shown from the ^{1}H NMR resonance at *ca.* δ 12 since the α-ketoaldehydes may be susceptible to undergo a benzil-benzilic acid rearrangement[120] in the presence of base.
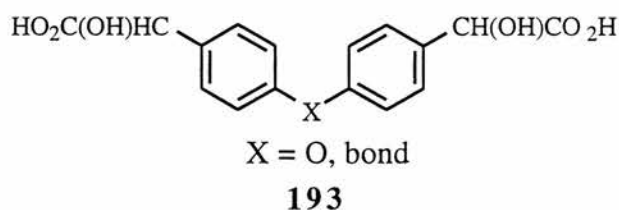
Since an oxidation procedure which was applicable both to oxidation at two sites and in principle to large scale synthesis was required, it was considered that the use of the reagents dimethyl sulphoxide and aqueous hydrobromic acid was attractive. The method of Floyd *et al.*[112] was therefore selected for use in the oxidation of diacetyl-aromatics to bis(α-ketoaldehydes). This method gave the bis-glyoxals in moderate to high yield and is now our preferred synthetic route to these compounds.

Diacetyl compound synthesis

The diacetyl compounds **194**,[121] **195**[122] and **196**[123] were therefore prepared in good yield by Friedel-Crafts acetylation of the aromatic compounds **197, 198** and **199** respectively with acetyl chloride and aluminium chloride in dichloromethane at room temperature.
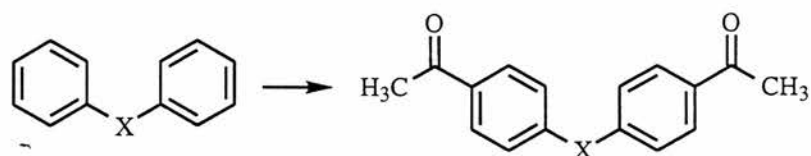
X = O   **197**   X = O   **194** 82%

X = bond **198**   X = bond **195** 64%

X = S   **199**   X = S   **196** 98%

Direct diacetylation of dibenzofuran and dibenzothiophene had not been previously reported in the literature. The literature procedures described the synthesis of 2,8-diacetyldibenzofuran **200** and 2,8-diacetyldibenzothiophene **201** by performing a mono-acetylation on **202**[124] and **203**[125] respectively to give the 2-acetyl compound and then reacting further to form the diacetyl compound. A 'one-pot' diacetylation was therefore developed and involved higher reaction temperatures (i.e. boiling in 1,2-dichloroethane) than the previous Friedel-Crafts reactions performed. The required diacetyl compounds were obtained cleanly and in good yield. Attempted diacetylation of dibenzofuran carried out at room temperature, however, resulted in mixtures of mono and diacetyl compounds.
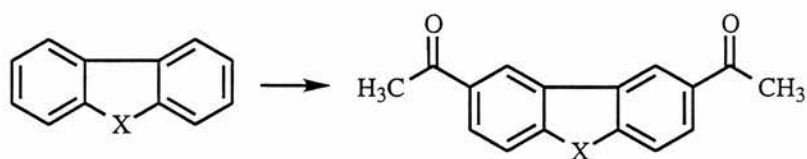
X = S **203**   X = S **201** 62%

X = O **202**   X = O **200** 90%

Bis-(4-acetylphenyl) sulphoxide **204** and bis-(4-acetylphenyl) sulphone **205**[126] were prepared from bis-(4-acetylphenyl sulphide) **206** using the oxidising agent magnesium monoperoxyphthalate in acetic acid. Bis-(4-acetylphenyl) sulphoxide **204** although being reported in the literature previously,[127] was not however characterised,

even by melting point, and was therefore treated as a new compound. However, microanalysis revealed there to be a small amount of impurity, possibly bis-(4-acetylphenyl) sulphone. Recrystallisation attempts made no difference to the purity of 204 obtained and it was decided to use the compound in crude form in further work. Bis-(4-acetylphenyl) sulphone appeared to have no contamination with partially oxidised products (by NMR and mass spectrometry).

X = SO	204	50%
X = SO$_2$	205	70%
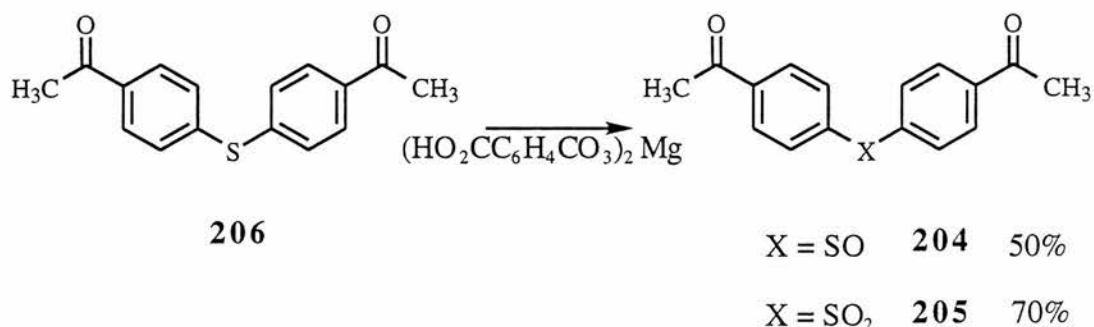
Oxidation of diacetyl compounds to bis-glyoxals

The diacetyl aromatics 194, 195, 200, 201, 204 and 205 were then oxidised using hydrobromic acid and dimethyl sulphoxide[112] to give the required bis-glyoxals in good yield. The bis-glyoxals 207,[128] 208 and 209[88] were water soluble and isolation required extraction with ethyl acetate, whereas the bis-glyoxals 15,[9] 210,[117] 211 and 212 were water insoluble and were isolated by filtration. The glyoxal 208 was not obtained in analytically pure form (as seen by incorrect microanalysis), the contamination was probably a trace of 207. It was important that the reaction temperature required for bis-glyoxal formation was maintained between 55–60°C, as demonstrated by trial reactions which were carried out to see if the reaction time could be decreased by increasing the reaction temperature to 80°C. When the reaction mixtures were poured into ice, brown oils were formed which were shown to be mixtures of many products by ^{1}H NMR and tlc.

The mass spectra either showed a molecular ion peak corresponding to the mass of the dihydrate species (207, 208, 211 and 212) or showed a molecular ion peak corresponding to the mass of the unhydrated species (15, 209 and 210). The

microanalysis of the bis-glyoxal **212** corresponded to the calculated value for the dihydrate species.
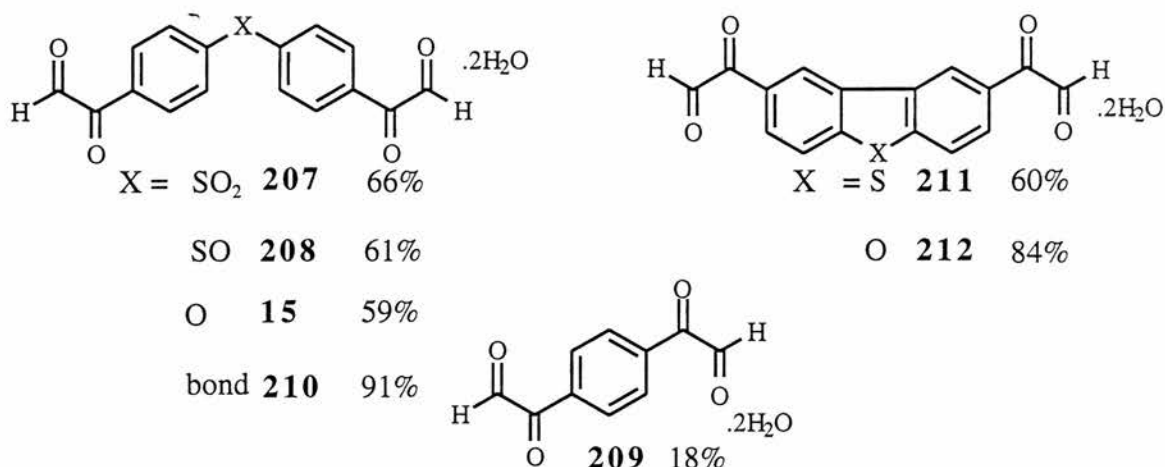
The bis-glyoxals were recrystallised from aqueous dioxan and were obtained in hydrated form as shown by their ^{1}H NMR spectra, where the formyl protons [RCH(OH)$_2$] resonate between δ 5.70 and 5.86 (see Appendix, table 1). Some of the bis-glyoxals **15, 210, 207** and **209** had been previously reported, and it was noticed that the literature melting points were often widely varying. On heating, the glyoxals turn yellow, possibly forming the unhydrated species, and different states of hydration and different rates of heating may account for the observed differences in melting points.

Bis-1,2,4-triazine synthesis

Reaction of the bis-glyoxals at room temperature with *S*-methylthiosemicarbazide, generated *in situ* from the corresponding hydriodide salt and sodium hydrogen carbonate, gave the corresponding bis-(3-methylsulphanyl-1,2,4-triazines) **213, 215, 216, 218** and **219** in acceptable yields. *S*-methylthiosemicarbazidium iodide was itself obtained by methylation of thiosemicarbazide using iodomethane.[98] Attempts to prepare the dibenzothiophene-containing analogue **217** have not proved entirely successful; although the product appears pure by NMR, it has not been obtained in analytical purity, and the nature and source of the impurity are as yet unknown. The bis-triazine **214** was also not obtained in analytical purity, with possible contamination with **213**.
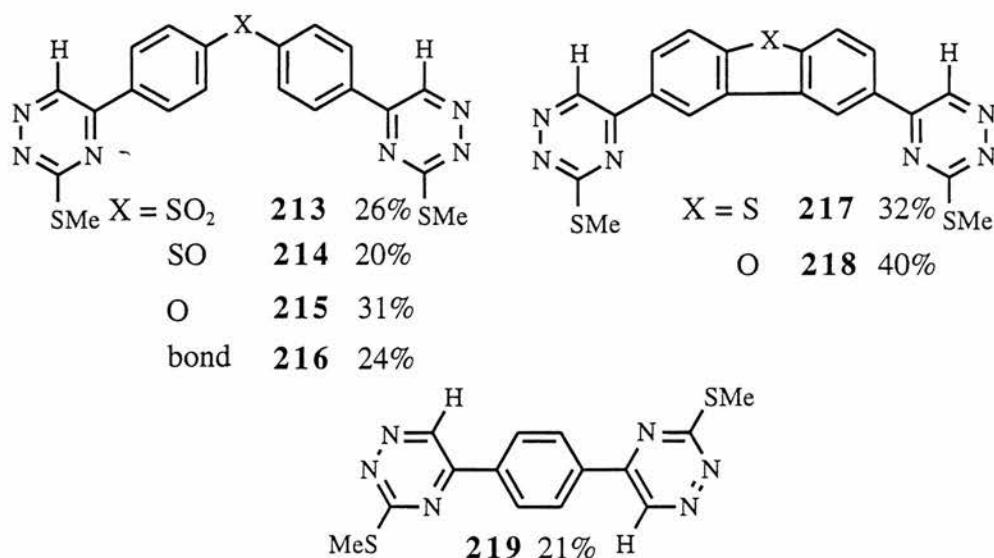
Most simple mono-glyoxals are soluble in water, and the literature method for their reaction with S-methylthiosemicarbazide involves water as the solvent.[94] Some of the bis-glyoxals **15**, **210**, **211** and **212**, however, are not readily soluble in water, and the solubility problems were partially aided by performing the reaction in aqueous ethanol (50%). An immediate orange colour on addition of the hydriodide salt to the reaction mixture was indicative of the reaction proceeding. No significant improvement in the yield of bis-1,2,4-triazine was observed when the purified glyoxals were used. It was however preferable to use the purified bis-glyoxals in triazine synthesis as purification of the resulting triazine was made easier. Attempts at carrying out the reaction at higher temperatures, for example in boiling ethanol, also made no significant improvement to yield of bis-triazine.

The purification of the bis-1,2,4-triazines by column chromatography [ether:petrol (40/60) 1:1] resulted in 'streaking' on the column, and hence purification by this method was abandoned. However, small scale purification by preparative tlc proved to be more successful and gave small (milligram) quantities of analytically pure bis-1,2,4-triazines. Attempted recrystallisation from ethanol gave powders which were judged to be pure by NMR, but microanalysis showed the percentage of nitrogen to be high (1%), perhaps because of a trace of unreacted S-methylthiosemicarbazide. Ethyl acetate/toluene

mixtures, however, proved to be a more successful recrystallisation solvent and gave the analytically pure bis-1,2,4-triazines as crystalline materials (see Appendix tables 2 and 3 for data of these compounds).

The bis-1,2,4-triazines show characteristic ^{1}H NMR peaks; the triazine ring proton (H-6) resonates between δ 9.38 and 9.53 and the methyl proton resonance occurs between δ 2.72 and 2.80. In the ^{13}C NMR spectra, the methyl group resonates at δ 13.9 to 14.0; the triazine C-3 between δ 173.7 and 174.4; the triazine C-5 between δ 152.5 and 154.1 and the triazine C-6 between δ 141.6 and 141.9.

The molecular ion is observed for each of the bis-methylsulphanyl-1,2,4-triazines in the mass spectra. The decomposition patterns for the bis-1,2,4-triazines **213**, **214**, **215**, **216** and **219** are postulated below and show the characteristic loss of 101 corresponding to the postulated loss of nitrogen and methyl thiocyanate.
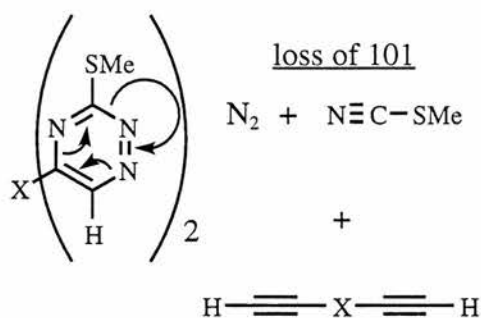
Flash Vacuum Pyrolysis of a bis-1,2,4-triazine

In order to establish whether this loss is a thermal decomposition or requires loss of one electron first and takes place in the mass spectrometer, a flash vacuum pyrolysis (FVP) of **215** was carried out. FVP has recently emerged as an important technique for the study of thermolysis reactions and involves sublimation of the substrate under high vacuum through a heated quartz tube. Since each molecule is only in the hot zone for a few milliseconds (the 'contact time') the technique is very mild, for example an FVP at 500 °C is equivalent to a temperature of less than 100 °C under solution thermolysis. In addition, since the substrate reacts in isolation, free from solvents, products or other substrate molecules, side reactions are normally avoided and products are normally

isolated in pure form. The FVP experiment resulted in the formation of methyl thiocyanate[129] in the trap and the bis-alkyne 220[130] in the furnace exit and therefore the FVP had proved that the bis-3-methylsulphanyl-1,2,4-triazines decompose thermally as postulated.
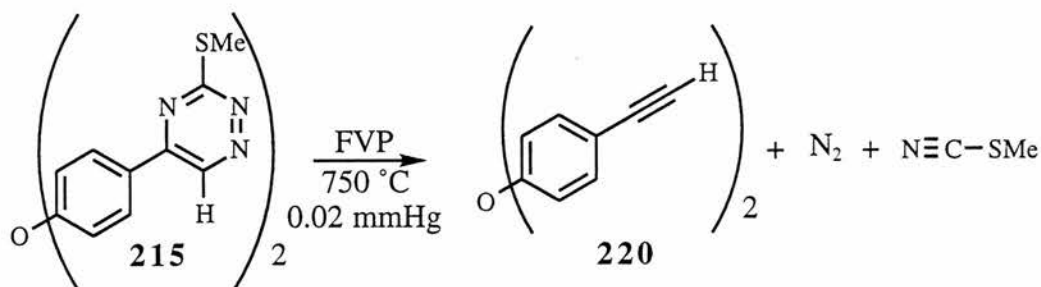
There are only a few reports of the thermolytic behaviour of 1,2,4-triazines found in the literature.[131] For example, the pyrolysis of tris(heptafluoroisopropyl)-1,2,4-triazine 221 at 650 °C afforded nitrogen, bis(heptafluoroisopropyl)acetylene 222 and perfluorobutyronitrile 223.[132]
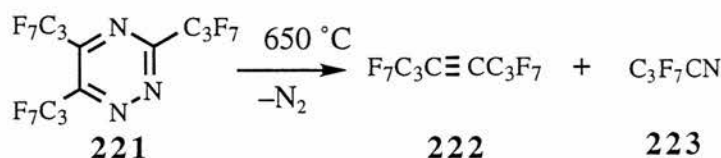
FVP had therefore provided a method of studying the thermolytic behaviour of the bis-1,2,4-triazines and since the bis-alkyne 220 was obtained in pure form, the technique may be useful for the synthesis of such compounds in general. The bis-1,2,4-triazines could be synthesised, their FVP carried out to give the alkynes and then the inverse electron demand Diels-Alder reactions could be investigated.

The choice of S-methylthiosemicarbazide as cyclising agent has the additional advantage that the 3-methylsulphanyl substituent can be oxidised to the corresponding methylsulphinyl or methylsulphonyl counterpart thereby increasing the electron-deficient nature of the 1,2,4-triazine and enhancing the postulated rate of participation in inverse electron demand Diels-Alder reactions.[50]

Oxidation of the methylsulphanyl substituents

Oxidation of methylsulphanyl groups to their methylsulphinyl and methylsulphonyl counterparts in 1,2,4-triazine chemistry is most commonly carried out by the use of *m*-chloroperbenzoic acid. A literature mono-1,2,4-triazine oxidation[66] was attempted from the sulphide **224** using *m*CPBA in order to establish a general method to sulphones and gave the required sulphone **225** cleanly and in good yield. The reactivity of the methylsulphonyl group in **225** as regards nucleophilic displacement was tested by a sodium methoxide displacement reaction which took place readily and in good yield at room temperature to give **226**.[80]
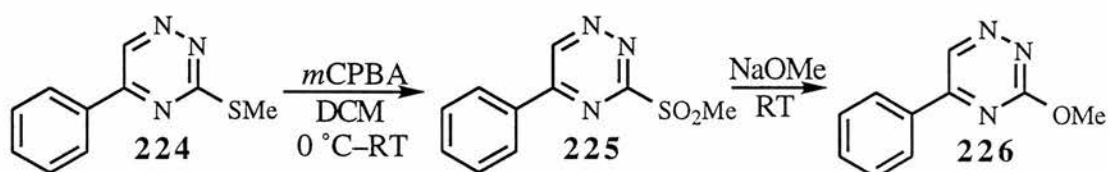
Complete oxidation of the bis-3-methylsulphanyl-1,2,4-triazines **215** and **216** to the bis-(methyl sulphones) **227** and **228** was attempted using an excess of *m*CPBA, however mixtures of sulphoxides and sulphones (sulphoxide:sulphone being approximately 1:3) were obtained and separation of these mixtures by column chromatography proved difficult as their R_f values were extremely similar. The bis-(3-methylsulphinyl-1,2,4-triazines) **229** and **230** were however obtained cleanly in good yield using 2.13 equivalents of *m*-chloroperbenzoic acid.

	X =	O	bond
SMe		**215**	**216**
SOMe		**230**	**229**
SO₂Me		**227**	**228**
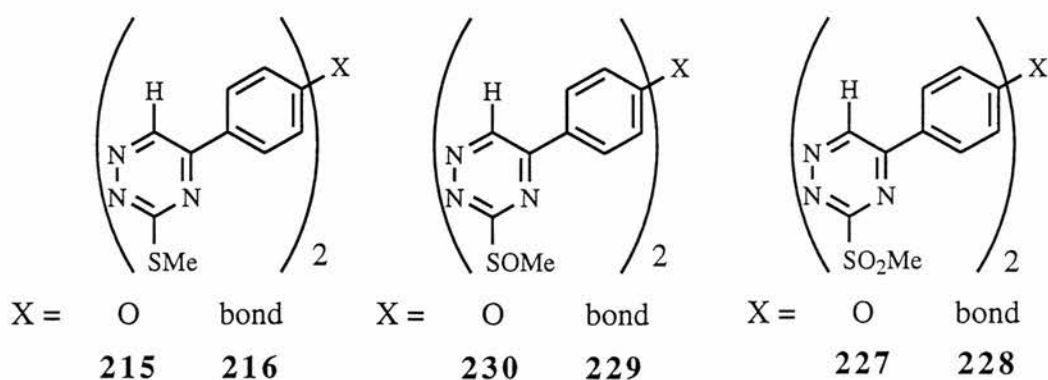
It was therefore necessary to look into various alternative oxidising agents for the conversion of sulphide to sulphone. Therefore the synthesis of bis-(3-methylsulphonyl-1,2,4-triazines) **227** and **228** was carried out using an adaptation of a published procedure for the oxidation of alkyl phenyl sulphides using the oxidising agent potassium hydrogen persulphate (a mixture containing 2 moles $KHSO_5$, 1 mole K_2SO_4 and 1 mole $KHSO_4$), commercially available under the trade name Oxone®. Trost and Curran reported[133] the use of oxone® in an aqueous methanol medium for the preparation of aliphatic sulphones, and recently, a report by Greenhalgh[134] revealed the oxidations of aliphatic compounds using oxone in wet alumina. This method proved to be successful for the synthesis of the bis-sulphones, 6 equivalents of oxone in refluxing chloroform being required to produce the sulphone; no contamination with partially oxidised products was observed. It was interesting to note that no reaction was observed in the absence of wet alumina. The bis-sulphoxides and bis-sulphones are all unstable, both thermally and on storage, and are extremely sensitive to moisture. The data for these compounds can be found in tables 4 and 5 of the Appendix.

The bis-sulphoxides show the characteristic peak for C-3 in the ^{13}C spectrum at δ 173, whereas in the bis-sulphones C-3 resonates further upfield (δ *ca.* 156). Purification of these compounds proved to be difficult; column chromatography was used, however the chromatographically pure compounds decomposed on storage at –20 °C under nitrogen to give sticky yellow tars. The compounds were therefore not obtained in analytical purity but were observed to be pure by NMR. These compounds were therefore best prepared immediately prior to use in further transformations.

Coupling reactions of preformed mono-triazines

Two different approaches to bis-1,2,4-triazines which involved the use of preformed mono-triazines were investigated in parallel.

• Coupling reactions involving a dimerisation process
• Mono triazine displacement reactions

<u>Coupling reactions involving a dimerisation process</u>

As discussed in the Introduction (pages 25–28), Paudler, Krass and Chen described the synthesis of 5,5'-bi-1,2,4-triazinyl derivatives by coupling of mono 1,2,4-triazines using sodium methoxide.[82] Whereas the treatment of 3-methylsulphanyl-1,2,4-triazine **115**[80] with sodium methoxide, which had been freshly generated by dissolving fresh sodium metal in absolute methanol, gave 3-methoxy-1,2,4-triazine, the addition of sodium metal to a solution of the 3-methylsulphanyl-1,2,4-triazine in dry methanol gave a higher melting material, shown by NMR to be 3,3'-dimethoxy-5,5'-bi-1,2,4-triazinyl **117**.[82] If the reaction was interrupted after 4 hours a small amount of the bis-(methylsulphanyl)-1,2,4-bi-triazinyl **116** was supposedly formed. We carried out a study of this reaction with monitoring by UV spectroscopy in order to establish whether the reaction if stopped at various different stages may give a sufficient yield of the bis-methylsulphanyl-1,2,4-bi-triazinyl for further study. However, although the reaction was quenched at many different stages the 3-methylsulphanyl dimer was only ever observed in very small quantities (approximately 5%) by NMR spectroscopy and hence this route was abandoned.

117

116

231
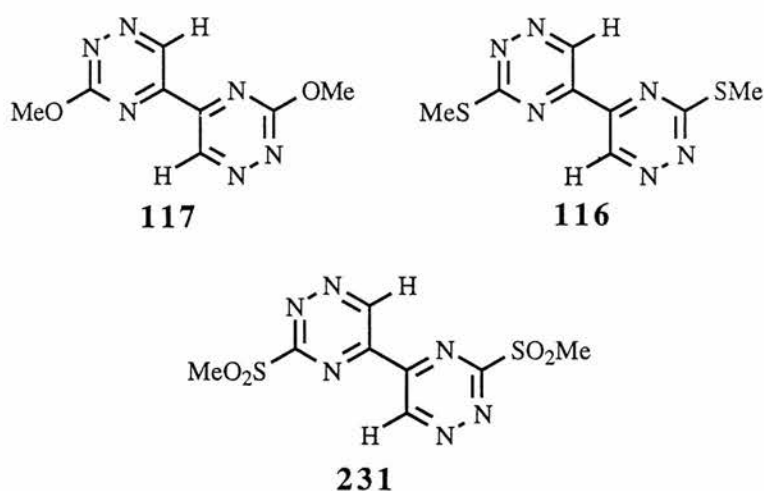
A method for the synthesis of these dimers was also attempted using the reported procedure which used potassium in liquid ammonia, however no experimental procedure was given and our attempts gave no reaction and starting material was recovered.[82]

Paudler and Chen also reported a dimerisation process of 5-unsubstituted 1,2,4-triazines in the presence of potassium cyanide.[81] The reaction sequence was followed as by the literature method and the required bis-methylsulphanyl-1,2,4-triazine **116** was formed in reasonable yield. The methylsulphanyl groups were then oxidised to their corresponding sulphones using potassium permanganate to give **231**. The oxidising agent *m*CPBA gave mixtures of sulphoxide and sulphone in the ratio 1:3 respectively. This route to bis-methylsulphonyl 1,2,4-triazines would, however, not be suitable for synthesis on a large scale as a five molar excess of potassium cyanide was required and hydrogen cyanide was evolved during the reaction. Therefore, this method for synthesis of 5,5'-bis-1,2,4-triazines is not preferable to that described earlier in which triazine rings were constructed at either end of a core unit.

Mono-1,2,4-triazine displacement reactions

Mono-1,2,4-triazine synthesis

In this approach to bis-1,2,4-triazines, preformed mono-triazines carrying one or two displaceable groups are the initial synthetic targets. 3,5-Dichloro-1,2,4-triazine **232** was considered to be an attractive starting material since it was envisaged that this molecule could serve as a reactive 'end-cap' for perhaps an amino-ended polyamide **233**.
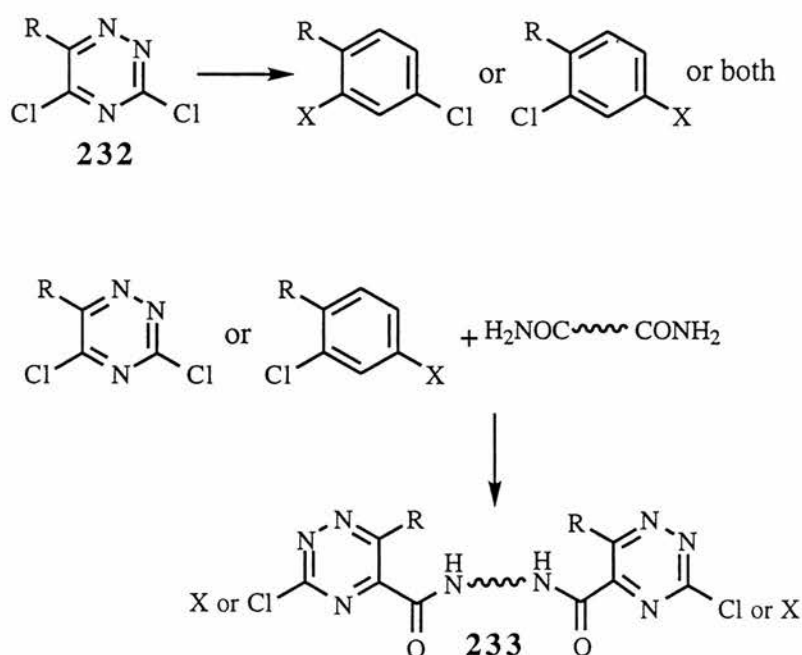
3,5-Dichloro-1,2,4-triazine **232** had been synthesised before by Grundmann *et al.*,[135] however a yield of only 10% was quoted. When Grundmann *et al.* studied the relative reactivity of the two halogens in this compound they considered that the 3-chloro rather than the 5-chloro was displaced by nucleophiles. Whereas, Taft and Shepherd studied[136] the reactivity of a series of 1,2,4-triazines bearing 6-alkyl and 3- and/or 5-chloro, methoxy, methylsulphanyl, -oxo, or -thioxo groups, and identified the 5-position as more reactive than the 3- toward nucleophilic substitution with, for example, sulphanilamide anion.

In order to establish a general route from triazinones to chlorotriazines, it was decided first to study the synthesis of 3-chloro-5-phenyl-1,2,4-triazine **234**.

The direct synthesis of 1,2,4-triazin-3-ones from glyoxals has been described in the Introduction (page 30). The initially formed semicarbazones can be isolated but direct formation of the triazin-3-one can supposedly be achieved by heating in acetic acid or with a base in ethanolic solution. However, many attempts to synthesise 5-phenyl-1,2,4-triazin-3-one **235** by heating phenylglyoxal **96** and semicarbazide hydrochloride[137] proved too unreliable, often giving poor yields of the correct product and producing mainly uncyclised semicarbazone.

The alternative method used via the 3-methylsulphanyl-1,2,4-triazine **224** proved to be more successful. Phenylglyoxal monohydrate **96** (prepared from acetophenone by oxidation with aqueous hydrobromic acid and dimethyl sulphoxide[112]) was reacted with *S*-methylthiosemicarbazide **148**[98] to form the 3-methylsulphanyl-1,2,4-triazine **224**. The hydrolysis step[138] occurred in good yield via **236** to give **235**.
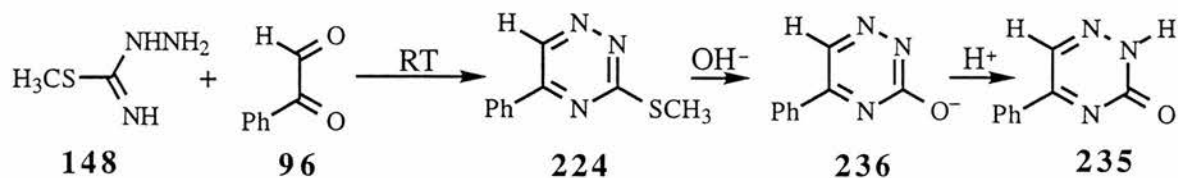
Conversion of the triazinone **235** into the chlorotriazine **234** was then attempted

using a method from the literature.[139] Many attempts using phosphoryl chloride, thionyl chloride and phosphorus pentachloride gave brown solids. Spectroscopic evidence revealed that only a small quantity of the desired chloro compound had been synthesised. An alternative route was thus sought. A method was thus devised and involved addition of triethylamine to the reaction mixture. This method gave the desired product in good yield.
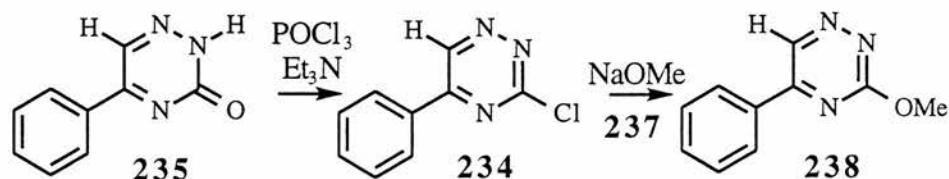
The reactivity of the chlorine towards nucleophilic displacement was tested by the reaction of the chlorotriazine with sodium methoxide 237 at room temperature, and this resulted in the formation of the methoxy derivative 238[80] in good yield.

3,5-Dichloro-1,2,4-triazine 232 was the next synthetic target. Firstly the synthesis of 6-azauracil (1,2,4-triazine-3,5-dione) had to be performed by a series of reactions starting from sodium mesoxalate.[140] When heated with thiosemicarbazide, the latter forms 1,2,4-triazin-5-one-3-thione-6-carboxylic acid 239, which was methylated using iodomethane and potassium hydroxide to obtain the 3-methylsulphanyl derivative 240. When heated with a mixture of concentrated hydrochloric and acetic acids, the thioether link was readily broken to yield 1,2,4-triazine-3,5-dione-6-carboxylic acid 241, which was then decarboxylated simply by heating in diphenyl ether to give 6-azauracil 242.
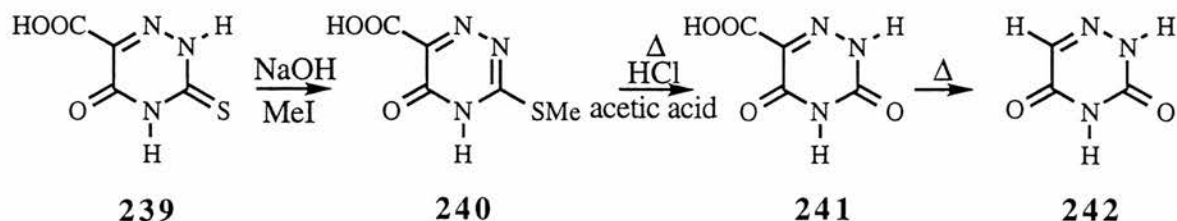
Many attempts at conversion of the 3,5-dione **242** to the 3,5-dichloro-1,2,4-triazine **232** involved the use of phosphoryl chloride, with and without triethylamine, and phosphorus pentachloride; however only a few of such attempts gave the correct compound, and the yield was at most 8%. It is not clear if the failure to obtain this material is due to its inherent instability (it is, of course, liable to undergo self-quaternisation), or to its reactivity towards nucleophiles (e.g. water), or to its volatility (perhaps creating problems in isolation of product). It was shown that no starting material was remaining (by tlc) and therefore it was concluded that it must be the instability of the product and not lack of reactivity of the starting material which caused the problems of low yield. It was therefore necessary to investigate an alternative mono-1,2,4-triazine for possible use in displacement reactions.
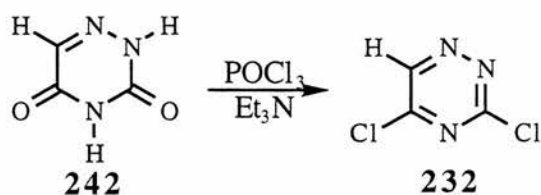
The synthesis of 3,5,6-trichloro-1,2,4-triazine **243** from **242**[141] however, proved more fruitful and gave the triazine in good yield. The triazine however begins to decompose after a day at 4°C and was thus stored at –20 °C (under nitrogen). The nucleophilic displacement by 1 equivalent of sodium methoxide resulted in substitution at the 5 position from ^{13}C NMR evidence and gave **244**.[142]
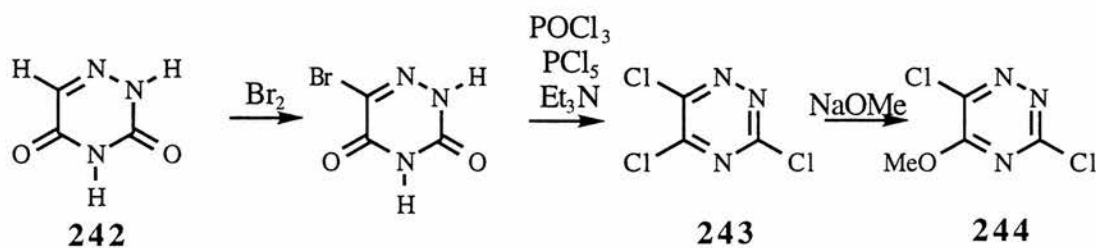
The following reaction sequence was attempted as it was thought that the triazine **245** would be a very useful mono triazine for displacement reactions. The reaction of

pyruvic acid **246** with thiosemicarbazide **110** gave **247**; treatment of this with phosphorus pentasulphide **248** gave the dithione derivative **249**, and the latter was then methylated using iodomethane and sodium hydroxide to give **250**.[143]
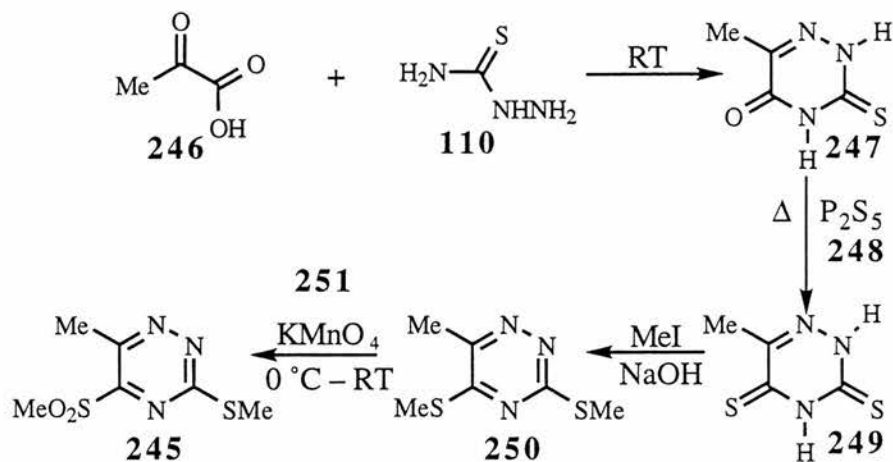
The first two steps were straightforward; however, the methylation was found to be very unreliable, often only giving small yields of the correct material. When however, the reaction vessel was shaken vigorously, the reaction was much more successful. Attempts at methylation using dimethyl sulphate were unsuccessful. The sulphide **250** was then oxidised at one position with the use of potassium permanganate **251** to produce a material which was shown to be a sulphone **245**.[144] The literature states that position 3 was oxidised, however from ^{13}C NMR evidence it can be seen that oxidation has taken place at position 5 since the C-5 resonance shifted upfield, whereas the shifts for C-3 and C-6 were virtually identical. The structure was also confirmed by a displacement of the methylsulphonyl group from **245** by sodium methoxide, the structure of the product confirmed by NMR and shown to be that of **252**.[145]
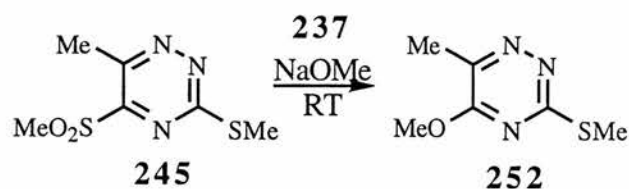
Bis-1,2,4-triazine formation

In order to establish a general reaction method for mono-triazine displacement reactions it was considered good practise to attempt a displacement using a triazine with only one displaceable group as illustrated below. This would also provide NMR data which would be useful in further reactions of this type. 3-Chloro-5,6-diphenyl-1,2,4-triazine **253**,[146] was synthesised from the reaction of benzil with semicarbazide hydrochloride and then chlorination of the resulting triazin-3-one **254**.[147] The addition of one equivalent of **253** to a solution containing one equivalent of sodium hydride and bisphenol A **255** resulted in the formation of **256** as expected.
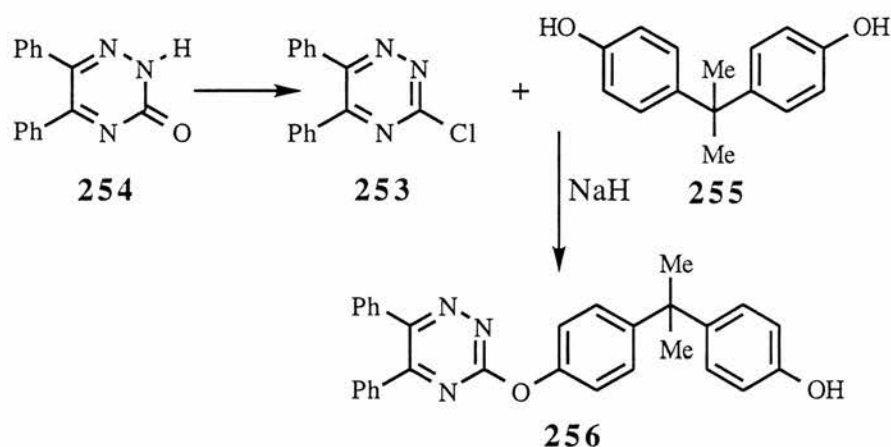
It was then decided to use 3,5,6-trichloro-1,2,4-triazine **243** in displacement reactions in the synthesis of bis-1,2,4-triazines. Although the reactivity of 3,5,6-trichloro-1,2,4-triazine has been reported,[142] no ^{13}C NMR evidence was given, and therefore in order to establish the preferential reactivity of positions 3, 5 and 6 towards nucleophilic attack and to obtain information on ^{13}C NMR shifts, the reaction of 3,5,6-trichloro-1,2,4-triazine with sodium methoxide was performed and resulted in replacement first at C-5 as shown by ^{13}C NMR (see page 54). Addition of two equivalents of 3,5,6-trichloro-1,2,4-triazine **243** to the dianion of bisphenol A (generated *in situ* in anhydrous tetrahydrofuran by treatment of bisphenol A **255** with 2 equivalents of sodium hydride) resulted in a poor yield of bis-1,2,4-triazine **257**.
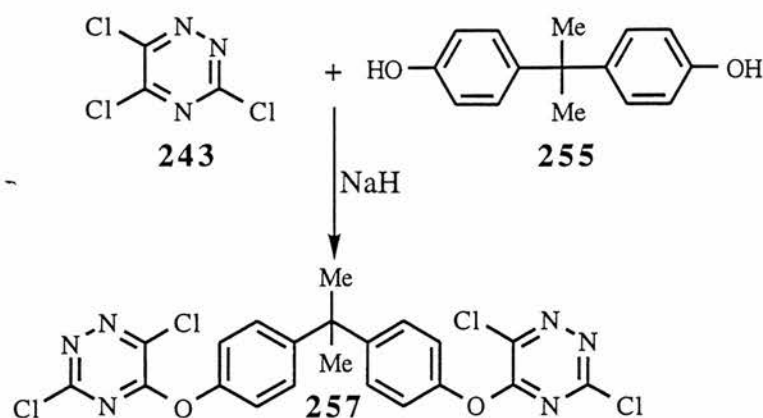
The structure was confirmed as being a 5,5'-linked bis-1,2,4-triazine system by examination of the ^{13}C NMR spectrum in which the C-3 and C-6 carbons resonated at similar values to the starting material, whereas the C-5 resonance was entirely different. Although a bis-triazine was formed, it was considered that as the yield of the final step was low (10%) and the reaction procedures more difficult, the preferred route to such compounds involved the construction of a triazine at either end of a core unit.

The reaction of **245** with bisphenol A **255** and sodium hydride was carried out similarly, however no bis-1,2,4-triazine **258** was formed; bisphenol A was recovered and the triazine decomposed. Attempts below room temperature gave no decomposition of the triazine, however no bis-1,2,4-triazine **258** was formed.
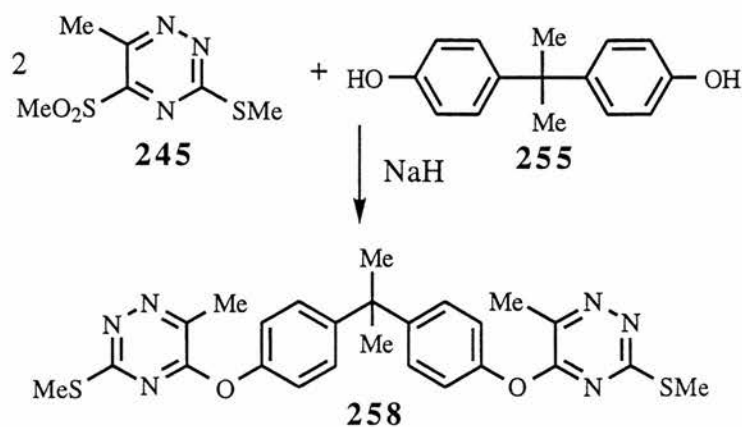
14. **Intermolecular Diels-Alder reactions**
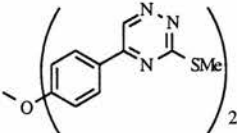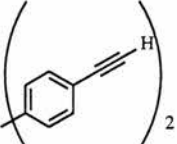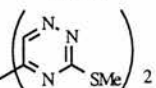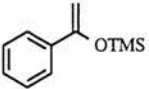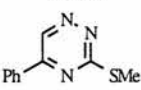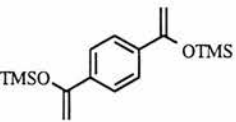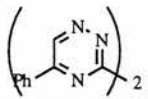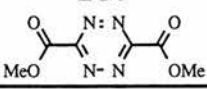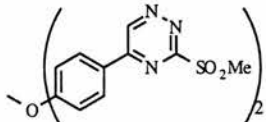
MOPAC calculations

In order for some idea of reactivity of various dienes and dienophiles to be established some molecular orbital calculations using the MOPAC computer program were carried out.

The semiempirical methods of quantum chemistry have been described and reviewed[15] with respect to the Diels-Alder reaction. Diels-Alder reactions with inverse electron demand were first proposed by Bachmann and Deno[148] and although a large number of high quality *ab initio* electronic structure calculations have been carried out,[149] it has only been feasible very recently to study, with accurate quantum mechanical methods, bonding in systems composed of more than twenty atoms, thereby making it possible to interpret and understand experimental data on many cycloadditions of interest to organic chemistry; for example the reaction of 3-phenyl-1,2,4,5-tetrazine with phenylacetylene was recently studied[150] using the Cray Y MP4/32 Supercomputer. The effect of substituents on the Diels-Alder reaction has been discussed in the Introduction and it was decided to carry out MOPAC calculations on a few molecules in order to establish for ourselves which combinations of diene and dienophile would be best for use in the inverse electron demand Diels-Alder reactions in this research project. The quantum mechanical Hamiltonian selected for use in this research work was AM1.[151] The dominant molecular orbital overlap in the inverse electron demand Diels-Alder reaction involves the LUMO of the diene and the HOMO of the dienophile and the energy of these orbitals would therefore provide evidence for postulated reactivity of a variety of combinations.

The MOPAC calculation results for a variety of dienes and dienophiles are represented in the table below. The compounds selected for study were chosen so that general trends in postulated reactivity could be established. The values for the energy were obtained from the MOPAC output file. The closer the HOMO and LUMO energy values, the more likely is a reaction to occur. The units for HOMO and LUMO energy

are in electron-volts.

DIENE STRUCTURE	LUMO ENERGY COEFFICIENT (eV)	DIENOPHILE STRUCTURE	HOMO ENERGY COEFFICIENT (eV)
17	−0.93549	**260**	−11.52223
215	−2.56437	**261**	−8.90367
116	−3.09575	**262**	−8.85072
236	−2.19866	**263**	−8.50743
99	−1.39198		
259	−3.54808		
227	−3.16524		

If we look first at the values calculated for the energy of the LUMO of the dienes, it can be observed that the oxidation of **215** to **227** results in a decrease in the LUMO

energy coefficient and therefore brings the LUMO closer to the HOMO of the dienophile and enhances the probability of an Diels-Alder reaction occurring. This theoretical observation is consistent with experimental fact as methylsulphonyl-1,2,4-triazines have been shown to be more reactive than the corresponding sulphide in an inverse electron demand Diels-Alder reaction, a fact that has been attributed to the electron-deficient nature of the sulphone. The energy coefficient for the bis-1,2,4-triazine **99** was as expected less negative due to the electron-donating groups which make the diene less electron-deficient which may result in this compound being less reactive in a Diels-Alder reaction with electron-rich dienophiles. The 1,2,4,5-tetrazine **259** has an energy coefficient which is closest to the dienophile's HOMO energy coefficients and would therefore be expected to be the most reactive diene in the set of calculations performed. 1,2,4,5-tetrazines are in fact considered to be one of the most reactive dienes for use in inverse electron-demand Diels-Alder reactions. If we turn to look at the values for the dienophiles, the energy coefficients suggest the following order of reactivity; ethylene **260** < alkyne **261** < enol ether **262** < bis enol ether **263**. The MOPAC calculations gave an indication of expected reactivity and suggested possible reactive combinations which could be carried out experimentally.

The following bis-1,2,4-triazines were used for all intermolecular Diels-Alder reaction attempts with the various dienophiles.

X =	O	bond	X =	O	bond	X =	O	bond
	215	**216**		**230**	**229**		**227**	**228**
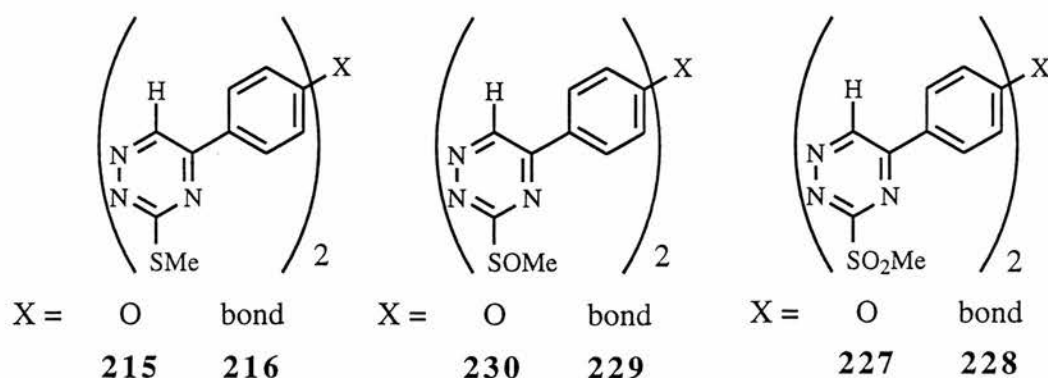
Bis dienophile synthesis: Diethynyl aromatics

<u>Mono alkyne synthesis</u>

Among the general routes to monoalkynes,[152] those which involve the transformation of methyl ketones are most appealing. The most attractive procedure involved the use of the Vilsmeier-Haack-Arnold reaction of an acetophenone **264** with phosphoryl chloride (2 mol. eq.) and *N,N*-dimethylformamide.[153,154] This gives the β-chlorocinnamaldehyde derivative **265** which is presumed to be the *E* stereoisomer[155] and loses formate and chloride to give the alkyne **266**. The *E*-**267** and *Z*- **268** isomers of the 3-chloropropenal are also illustrated below.
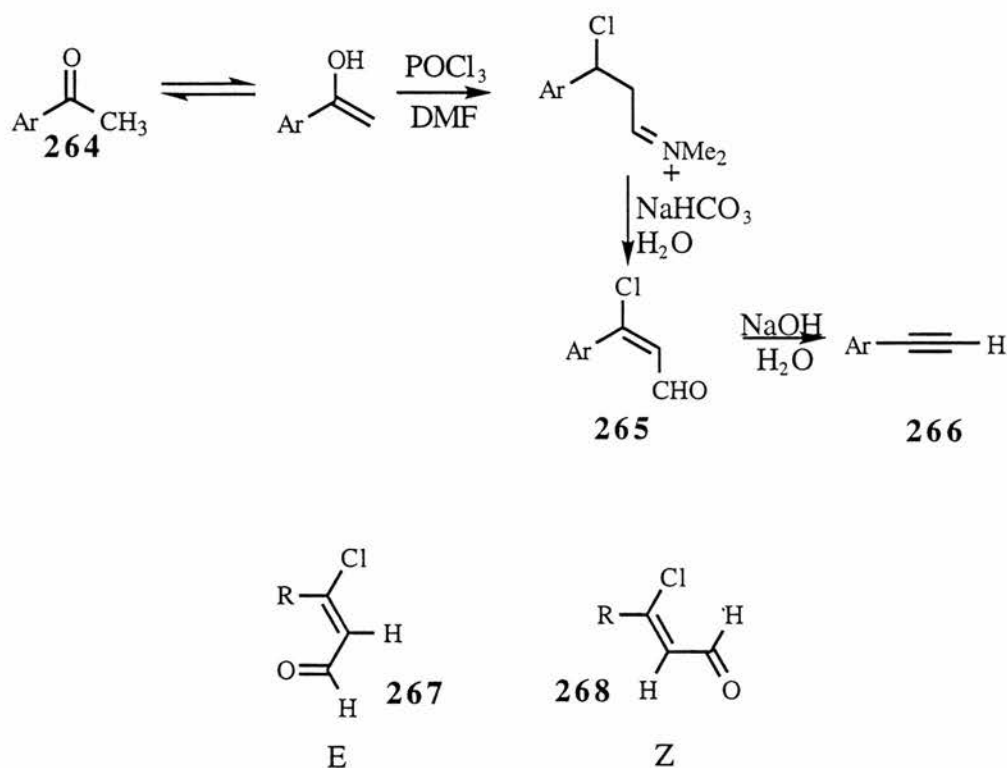
The proposed mechanism for alkyne synthesis is shown below. Assuming **269** is fully delocalised, there is a possibility of an equilibrium between **270** and **269** and chloride will add in such a way that loss of dimethylformamide will yield the thermodynamically most stable mixture of isomers.
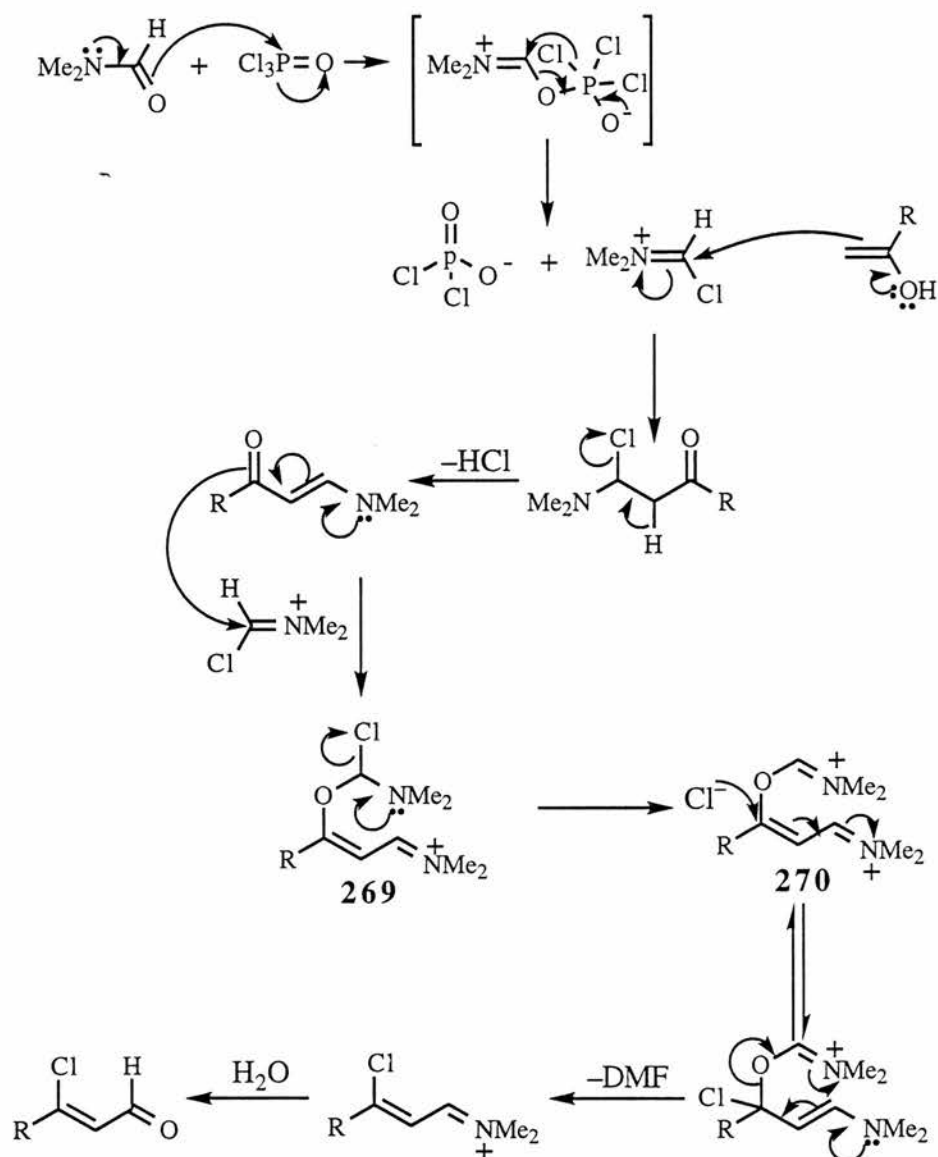
Bis-alkyne synthesis

A route has been established within the research group[156] to bis-alkynes based on the above Vilsmeier-Haack-Arnold reaction. This method was used in preference to literature methods[130,157,158] for bis-alkyne formation which often either involve the use of expensive catalysts, are low yielding or involve the use of strong bases.

The use of the Vilsmeier reagent can be further exemplified by the route to ethynyl-terminated ether-ketone-sulphone oligomers **271** and polymers.[159-161]

$X = ` —C≡C-H$
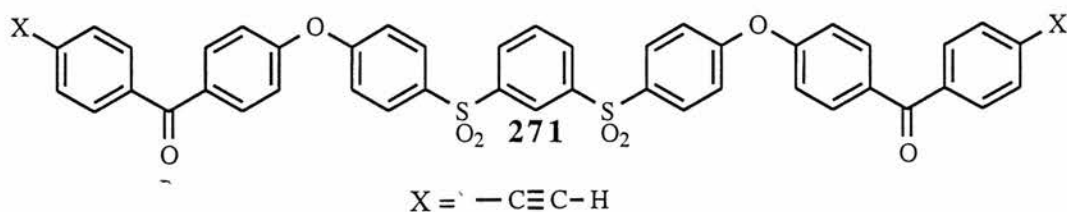
The reaction sequence in use in the group is shown below. A 4-equivalent excess of the Vilsmeier reagent was required to give the bis-3-chloropropenals **272** from the diacetyl aromatics **169** and loss of formate and chloride gave the bis-alkynes **273**.
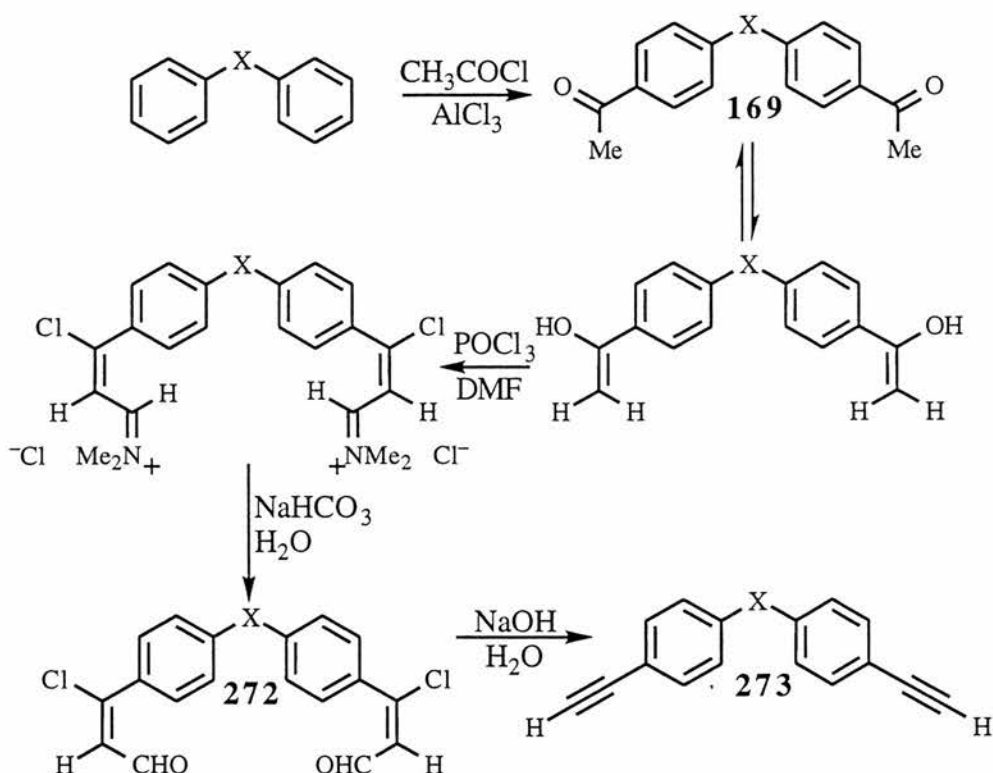
For the purpose of this present work, the bis-alkynes **220** and **274** were synthesised from the corresponding diacetyl aromatics.[121,123] Attempts at purification of the bis-3-chloropropenals **275** and **276** by reprecipitation proved difficult; they were judged to be of sufficient purity by NMR and to consist apparently of a single isomer (*E,E*) and were converted into the alkynes without further purification. Purification of the bis-alkynes by dry flash column chromatography[162] gave the required bis-alkynes which are readily recognised by their characteristic infrared spectral peaks at 3260–3310

cm^{-1} and 2100–2110 cm^{-1}.

X = O   **194**

X = S   **196**

X = O   **275**

X = S   **276**

X = O   **220**

X = S   **274**
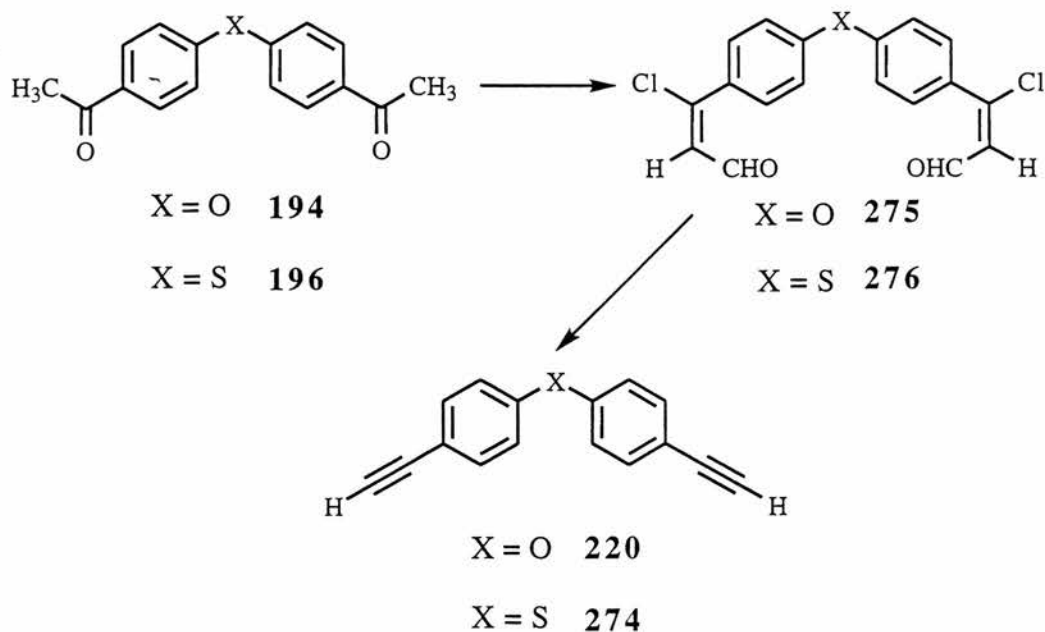
Intermolecular Diels-Alder reaction attempts with bis-alkynes

The bis-alkynes **273** can be reacted in an intermolecular inverse electron demand Diels-Alder reaction with the bis-3-methylsulphonyl-1,2,4-triazines **167** as a synthetic approach to heteroaromatic polymers **277**.
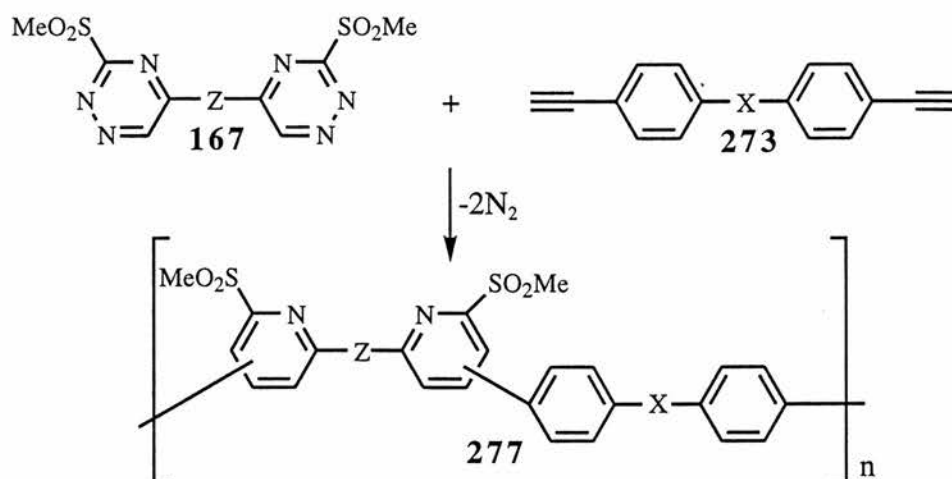
Several trial Diels-Alder reactions were carried out using phenylacetylene **278** as dienophile with the bis-1,2,4-triazines **215**, **229** and **227** in boiling dioxan, however

no reaction was observed.

MOPAC calculations had shown that the value for the HOMO energy coefficient for the bis-alkyne **220** was less negative than that for phenylacetylene and would therefore be expected to be more reactive in an inverse electron demand Diels-Alder reaction with, for example, a bis-1,2,4-triazine. The following reaction attempts of Diels-Alder reactions between bis-1,2,4-triazines and bis-alkynes were carried out. The sulphone **227** was reacted with the alkynes **220** and **274** by heating in dry dioxan for several days; however, no Diels-Alder reaction took place in any of the attempts. Higher reaction temperatures were then used; however, once again no reaction took place. The concentration of the reaction mixture was then increased in order to obtain closer molecular contact, however no reaction was ever observed. Similar results were obtained when the sulphone **228** was reacted under the same reaction conditions. Following the reaction by tlc revealed the appearance of several small new spots, however, these were shown by NMR not to be cycloaddition products, but instead to consist of possible decomposition products.

Since the sulphone apparently decomposed under such extreme reaction conditions, the sulphoxides **229** and **230** were used instead as they seemed to be less unstable to heat and might therefore be capable of reacting in a Diels-Alder reaction before decomposition. Reactions with bis-alkynes **220** and **274** were carried out with variations in reaction time, reaction temperature and concentration of reaction mixture; however once again no Diels-Alder reaction product was obtained. NMR and tlc showed that the starting materials were unchanged.

An attempt at reacting the bis-(methylsulphanyl-1,2,4-triazines) **215** and **216** in a Diels-Alder reaction with the bis-alkynes **220** and **274** for 1 week in refluxing nitrobenzene (b.p. 210°C) gave no cycloaddition product and the starting materials were recovered unchanged. The aforementioned combinations were also heated together without solvent in a sand bath at 250°C, however once again no reaction occurred and starting materials were recovered.

The attempted Diels-Alder reaction of **231** with phenylacetylene also resulted in no

reaction taking place.

231
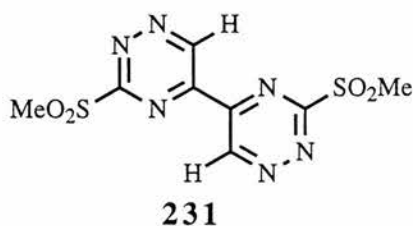
Intermolecular Diels-Alder reaction attempts with enol ethers

The reactivity of enol ethers has been demonstrated with regards to Diels-Alder chemistry. Sauer demonstrated[40,41] that an enol ether **262** can add across C-3/C-6 of the 1,2,4-triazine nucleus **279** to afford pyridine products **280**.
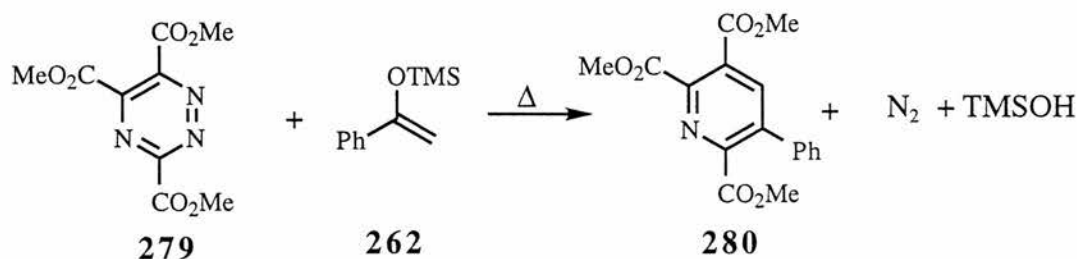
The MOPAC calculations had demonstrated that the enol ether **262** was more likely to react with the bis-1,2,4-triazines than the alkynes and was therefore used for model studies. The following Diels-Alder reaction attempts were carried out. The sulphone **227** was reacted with the enol ether **262** in boiling dry dioxan for several days, however, no reaction was observed to take place. Higher reaction temperatures and increased concentration of the reaction mixture were used, however, no reaction was ever observed. Similar results were obtained when the sulphone **228** was reacted under the same reaction conditions.

262
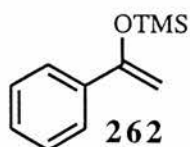
The bis-3-methylsulphinyl-1,2,4-triazines **229** and **230** were also reacted with **262** with wide variations in reaction time, reaction temperature and concentration of reaction mixture being carried out; however once again no Diels-Alder reaction product was obtained, NMR and tlc showing that the starting materials were unchanged.

An attempt at reacting the bis-(methylsulphanyl-1,2,4-triazines) **215** and **216** in a Diels-Alder reaction with **262** for 5 days in refluxing nitrobenzene (b.p. 210°C) gave no cycloaddition product and the starting materials were recovered unchanged. The Diels-Alder reaction attempts with enol ethers were not explored further and it was decided to attempt Diels-Alder reactions with enamines.

Dienophile synthesis: Mono enamines

Mono enamine synthesis

Enamines, or α,β-unsaturated amines, are useful synthetic intermediates whose reactivity is illustrated below. One of the most important methods for the synthesis of enamines involves heating an aldehyde or ketone with a secondary amine, usually pyrrolidine or morpholine, in an inert solvent, with provision for removal of the water formed.
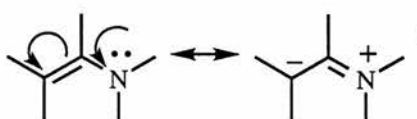
The reactivity of enamines in the inverse electron demand Diels-Alder reaction has been covered in the Introduction (pages 13–14). Enamines are in fact one of the most reactive dienophiles for use in Diels-Alder reactions with electron-rich dienophiles. It was thought that the synthesis of bis-enamines **281** and their subsequent reaction with bis-1,2,4-triazines **282** in the inverse electron demand Diels-Alder reaction, with loss of nitrogen and pyrrolidine, would result in a polymer **283**.
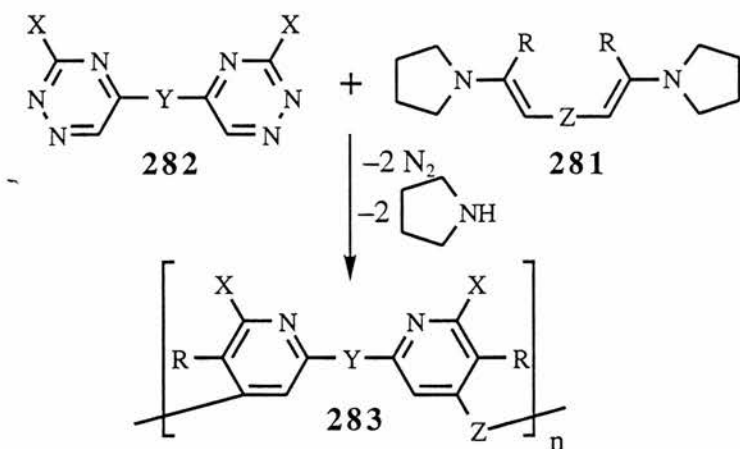
In order for trial reactions involving bis-1,2,4-triazines and enamines to be carried out, the mono enamine **284** was synthesised for trial reactions from cyclohexanone **285** and pyrolidine **286**.[163] As this compound was relatively unstable it was stored under nitrogen in the freezer and purified by distillation prior to use.
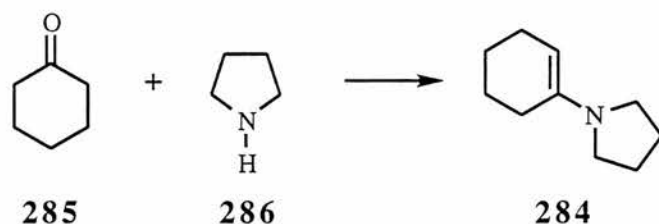
Intermolecular Diels-Alder reaction attempts with mono enamines

The following reaction attempts were carried out using the bis-1,2,4-triazines and the enamine **284** and are illustrated overleaf. A reaction between **284** and the bis-sulphone **227** was carried out in boiling dioxan for 24 hours and resulted in decomposition products. Since decomposition of the triazine had occurred, the enamine was added to the triazine **227** at 0°C, however, once again no Diels-Alder reaction product was observed and starting materials were recovered. The bis-sulphoxide **230**, in contrast, underwent a Diels-Alder reaction at 0°C with **284** to give **287**. The bis-sulphide **215** did not react with the enamine at 0 °C or in boiling dioxan for 4 days and was recovered.
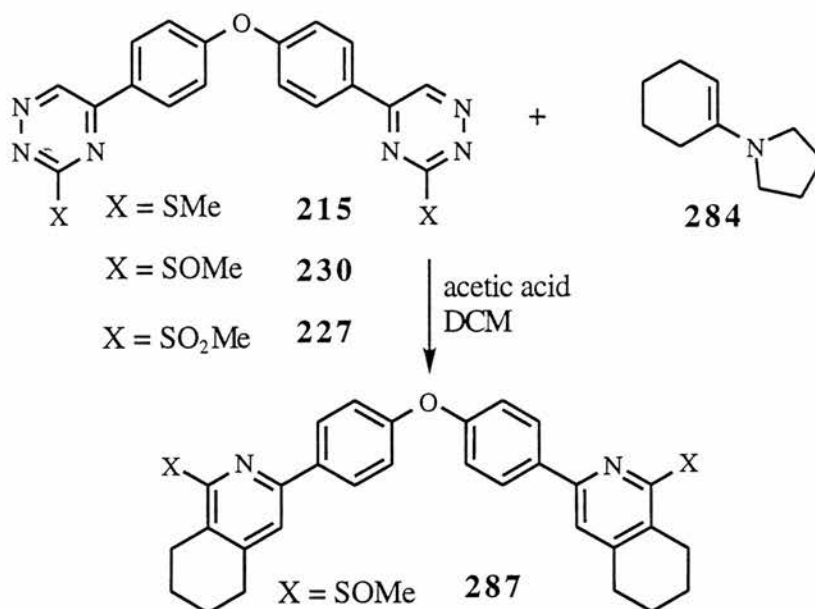
In Situ oxidation and attempted Diels-Alder reaction of a bis-triazine

An attempt at an oxidation of **215** with *m*CPBA to give **227** and an *in situ* Diels-Alder reaction with **284** as dienophile was attempted in order to avoid the problems encountered due to the instability of the bis-1,2,4-triazine sulphones. However, once again no Diels-Alder reaction products were observed.

Since it had been demonstrated that the bis-sulphoxide **230** reacts with a mono-enamine, it was decided to synthesise a bis-enamine in order for polymers to be made. Synthetic routes to bis-enamines were therefore investigated. .

Bis dienophile synthesis: Bis enamine synthesis

The synthesis of a bis-enamine **288** was attempted as shown from the reaction of bis-4-(acetylphenyl ether) **194** with pyrrolidine **286** in boiling toluene with a catalytic amount of *p*-toluenesulphonic acid added. A black tar was however formed and was shown to consist of starting material and a black film which is unidentified. A reaction attempt without *p*-toluenesulphonic acid gave similar results.
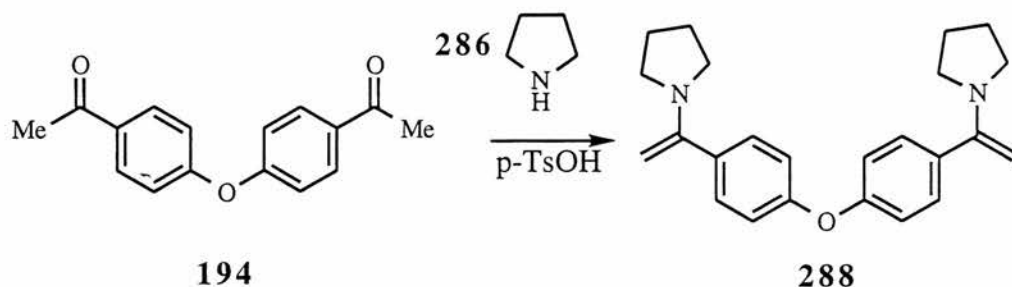
It was then considered that the formation of the bis-enamine **289** could be achieved by the reaction sequence shown below making use of the Wittig reaction.
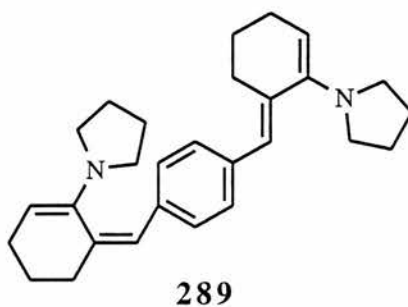
The phosphorus ylid (which is a hybrid of two canonical forms) was prepared by heating the phosphonium salt **290** in t-butanol with potassium t-butoxide to give **291**,[164] and the subsequent reaction with terephthaldehyde **292** should then result in **293** being formed. The reaction of **293** with pyrrolidine should result in the synthesis of bis-enamine **289**.
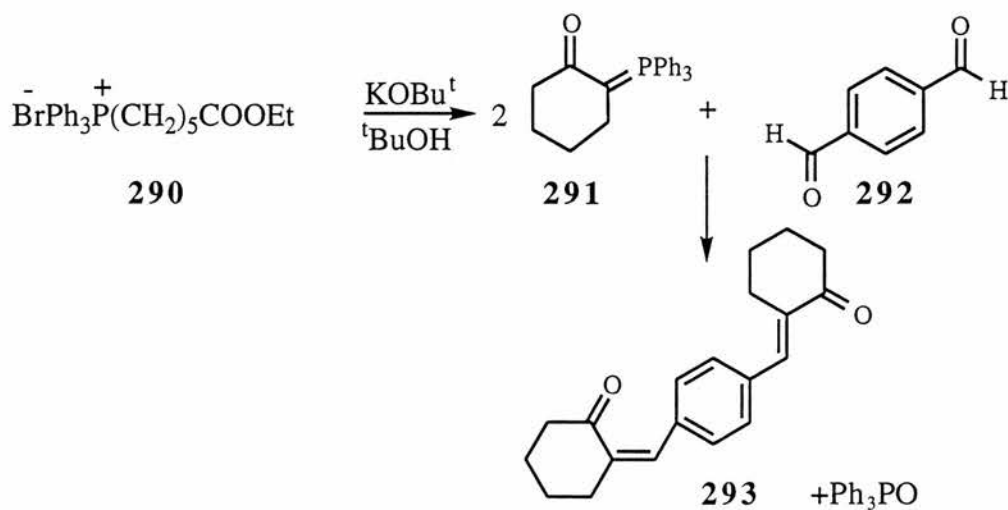
However, the reaction of the ylid with terephthaldehyde resulted in **294** being formed. Despite many attempts varying reaction time and temperature, only a very small amount of **293** was ever obtained.

294
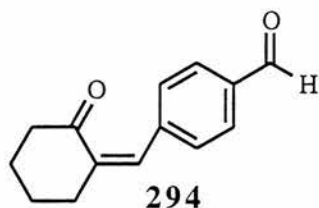
The following synthetic procedure was therefore devised for the synthesis of **289**. The addition of cyclohexanone **285** to terephthaldehyde **292**, using lithium diisopropylamide as base, gave **295**, and the dehydration using *p*-toluenesulphonic acid gave **293** in good yield. It was necessary to maintain the reaction temperature at 0°C throughout the dehydration step since a black solid was seen to form around the sides of the flask when higher reaction temperatures were used, and this resulted in decreased yields of the desired reaction product. The bis-enamine **289** could then be formed from the reaction of **293** with pyrrolidine and used *in situ* in an attempted Diels-Alder reaction.
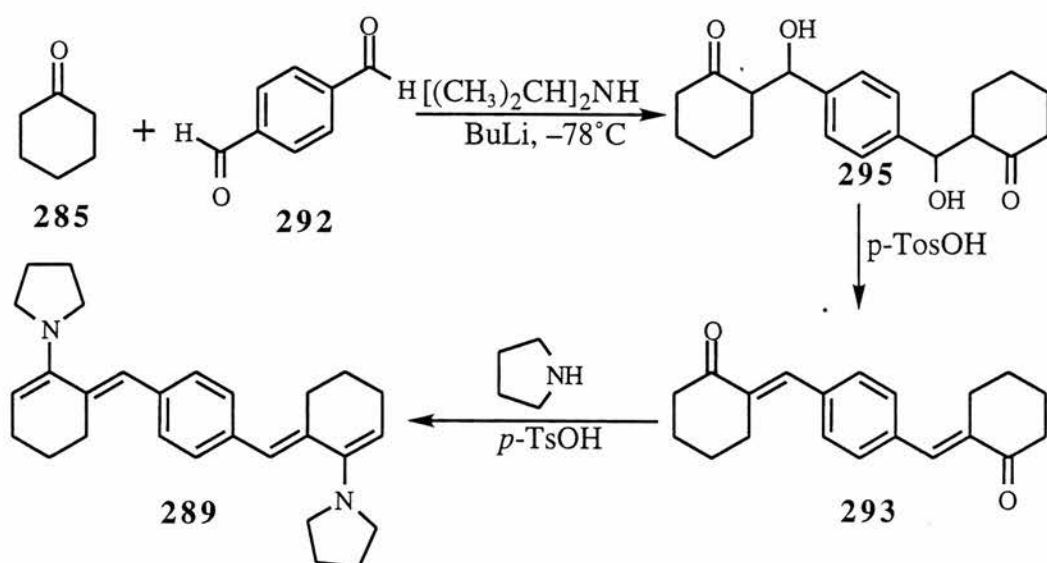
The above reaction sequence was relatively simple to carry out and gave good yields at each stage except the last. The formation of the bis-enamine was only confirmed by running NMR spectra on the reaction mixture *in situ* and not by isolation of the product. All attempts at isolation proved unsuccessful and resulted in decomposition of the bis-enamine. Unfortunately attempts at *in situ* intermolecular Diels-Alder reactions using the bis-sulphoxide **230** and the bis-enamine **289** proved unsuccessful.

Therefore, in conclusion it has been demonstrated that the bis-1,2,4-triazines **215**, **216**, **227**, **228**, **229** and **230** are not electron-deficient enough in general to participate in intermolecular inverse electron demand Diels-Alder reactions with a variety of dienophiles under normal reaction conditions of temperature and pressure. It may therefore be necessary to carry out these reactions at increased pressure. Diels-Alder reactions show large negative entropies of activation in line with the rigid transition state of the concerted mechanism. The large negative values for activation volume which are observed indicate that the transition state is smaller than the reactants and therefore as a consequence the Diels-Alder reaction is favoured by an increase in pressure.[165]

15. **Intramolecular Diels-Alder reactions**

Professor Taylor's group at Princeton showed that if a dienophile is tethered to the triazine ring through any of the three ring carbon atoms, then proved the tether is of the appropriate length, an intramolecular Diels-Alder reaction will occur.[61] These reactions were to be used as models towards the synthesis of a new aromatic/heteroaromatic polymer **296**, in which the key intermediates are bis-(3-methylsulphonyl-1,2,4-triazines) **167** and bis-(*o*-ethynylphenols) **297**.

The example shown **296** is merely representative of a large family of related polymers since the synthesis is capable of many variations. The elongated, rigid benzfuro[2,3-*b*]pyridine unit may confer for example liquid crystallinity on this type of polymer and the materials produced may display attractive properties.
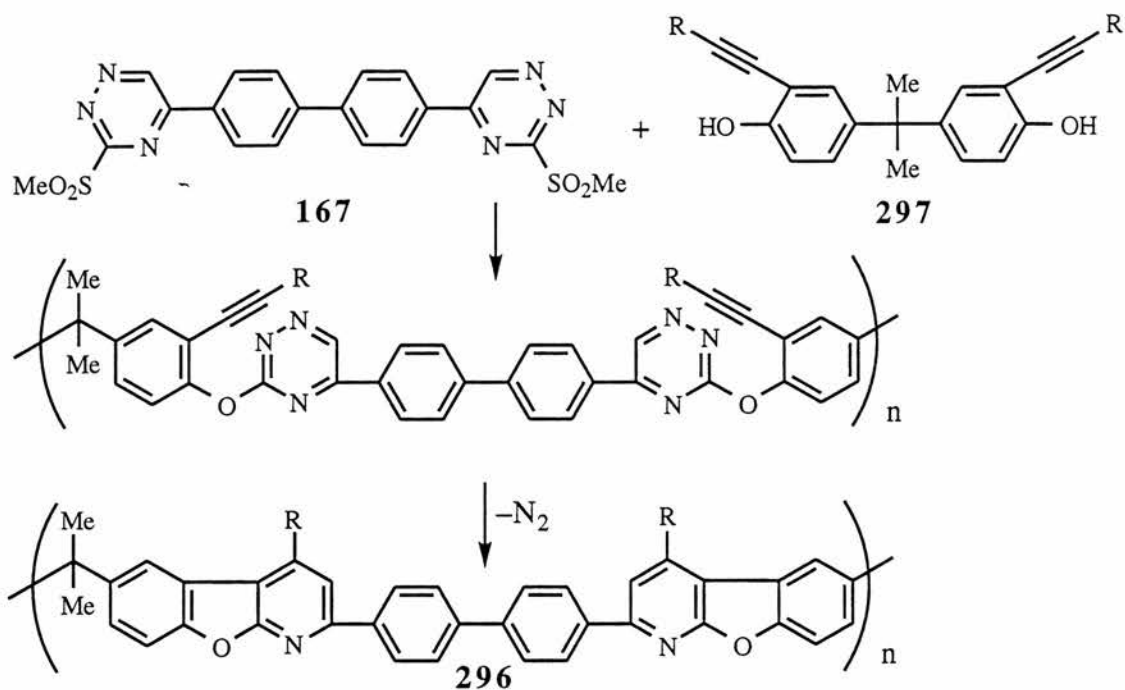
Palladium catalysed coupling reactions

Palladium catalysed coupling reactions of vinyl halides and aryl halides to alkenes in a Heck reaction[166] have found widespread interest in the current literature.[167] For example, compounds containing an acetylenic hydrogen atom **298** can be readily substituted by organic halides **299** such as alkenyl,[168] aryl, acyl[169] halides in the presence of copper (I) iodide and bis(triphenylphosphine)palladium dichloride in amines to give **300**.
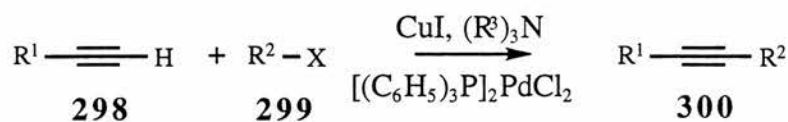
In an attempt to use the method for the preparation of terminal acetylenes, for example, aryl iodides were reacted with a large excess of acetylene gas, however the major product was the disubstituted acetylenic compound. However when one end of **301** was protected with a trimethylsilyl group using **302** and the unprotected end was then coupled to a suitable halide, the mono acetylenic compound **303** was formed. The

trimethylsilyl group was used as protecting group because it can be quantitatively removed by treatment with dilute alkali to give **304**.[170]
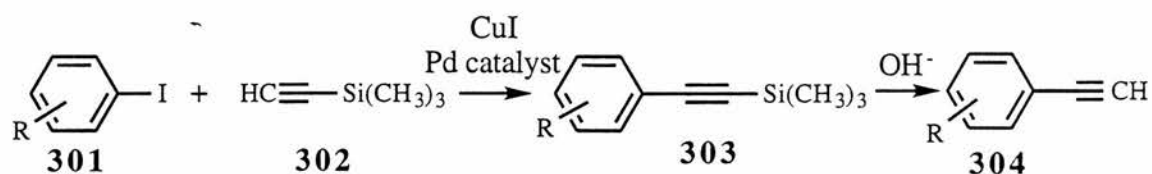
Synthesis of bis-*o*-ethynylphenols

The synthesis of bis-*o*-ethynylphenol **305** from bis-*o*-bromophenols **306** and alkynes in the presence of a palladium catalyst **307** has been attempted using an adaptation of reaction conditions described by Sagi *et al.*.[64] In their work the *o*-iodophenyl ether **308**, prepared by condensation of *o*-iodophenol **309** with **310** and then reaction with terminal acetylenes over PdCl$_2$(PPh$_3$)$_2$ to give **311**. These phenyl ethers subsequently underwent an intramolecular Diels-Alder reaction to give **312**.
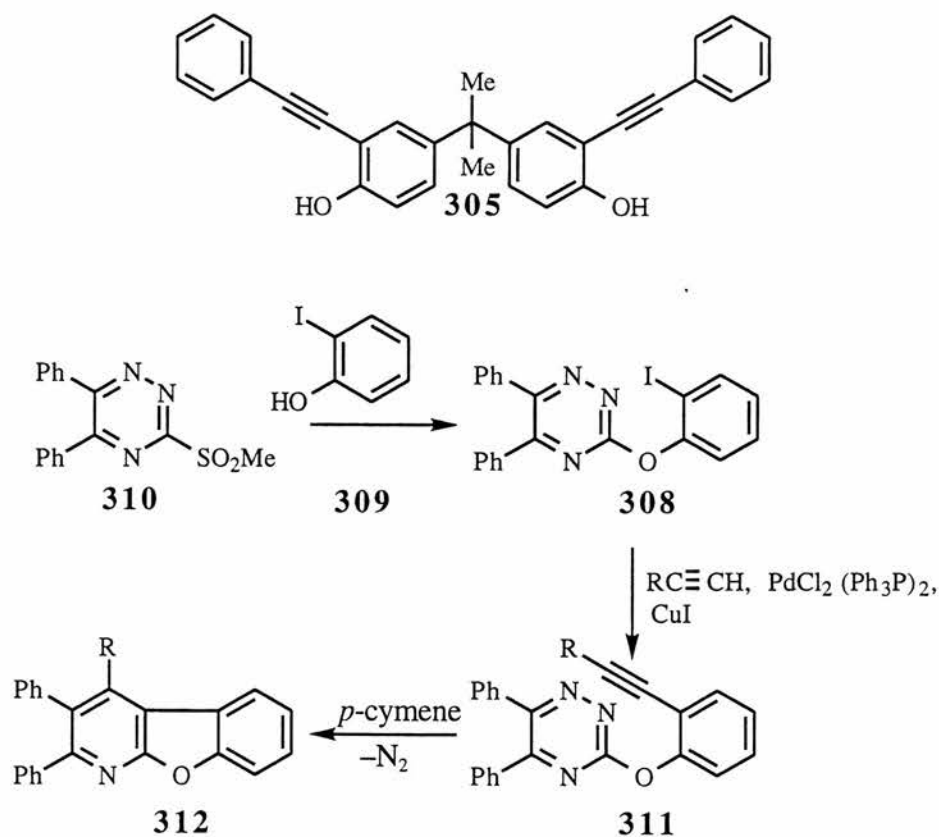
The synthesis of bis-*o*-ethynylphenols **305** was attempted therefore by the route shown below. The first reaction step involved bromination of bisphenol A **255** to give **306**. A patent by Thompson[171] described the synthesis of 2,2'-dibromobisphenol A, however no experimental details were given. Attempted reaction below or at room temperature gave a purple solid which was shown to be a mixture of 2-monobromobisphenol A **313** and 2,2'-dibromobisphenol A **306** by NMR. Marks and Sekinger have recently reported[172] a study of the halogenation of bisphenol A and discussed the bromination of bisphenol A in methanol at or below room temperature as producing the entire family of bromination products, i.e. 2-mono-, 2,2'-di-, 2,2',6-tri- and 2,2',6,6'-tetrabromobisphenol A.
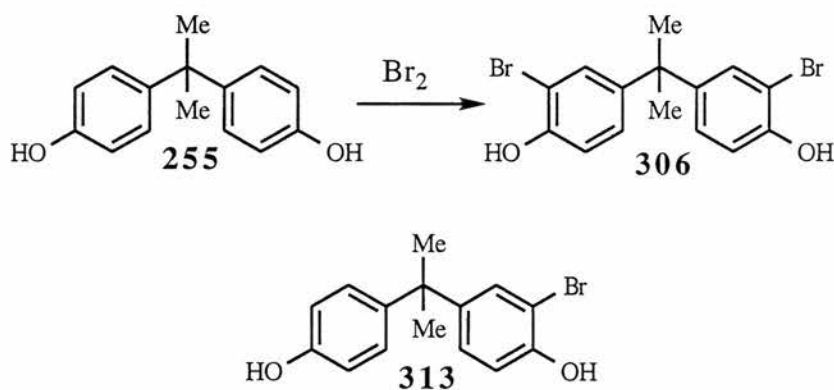
After removal of hydrogen bromide (a by-product of the electrophilic aromatic substitution reaction), by a nitrogen purge and a modified work-up procedure, the amount of side products formed was reduced and pure 2,2'-dibromobisphenol was synthesised in good yield. The regiochemistry was confirmed by mass spectrometry in which a molecular ion peak at 384 amu with a two bromine isotope pattern was observed. Fragmentation ions at m/e 275 and 197 are observed and can be attributed to monobrominated radicals, the former arising from two methyl radical losses from the molecular ion; and the latter arising from loss of the monobromovinylphenol radical. In addition, no fragmentation ions which correspond to non-brominated or dibrominated radicals are observed and therefore, the mass spectral data prove the presence of one bromine atom per phenyl ring.

It was proposed that **306** would react with phenylacetylene **278**, dichlorobis(triphenylphosphine)palladium **307**, copper (I) iodide **314** and triethylamine as shown in the figure below to give **305**.

Copper (I) iodide **314** was freshly prepared by the reaction sequence shown below[173] from copper sulphate, potassium iodide and sodium thiosulphate. Since copper(I) readily converts to copper(II) it was necessary to prepare it immediately prior to use and store it in the dark.

$$2\,CuSO_4 + 4\,KI + 2\,Na_2S_2O_3 \longrightarrow 2\,CuI + 2\,K_2SO_4 + Na_2S_4O_6 + 2\,NaI$$
314

$$2\,CuSO_4 + 4\,KI \longrightarrow 2\,CuI_2 + 2\,K_2SO_4$$
$$2\,CuI_2 \longrightarrow 2\,CuI + I_2$$
$$2\,Na_2S_2O_3 + I_2 \longrightarrow Na_2S_4O_6 + 2\,NaI$$

The catalyst dichlorobis(triphenylphosphine)palladium **307** is generally used in the carboalkylation of halides to carboxylic acids and amides. The following reaction sequence has been postulated for the coupling of copper(I) arylacetylenes with iodoarenes or iodoalkenes[168] in a Stephans-Castro coupling reaction.[174] Although the detailed mechanism has not been clarified, it seems likely that the substitution occurs through an initial formation of bis-(triphenylphosphine)dialkynylpalladium (II) **315** which gives a catalytic species, bis(triphenylphosphine)palladium (0) **316**, by means of a reductive

elimination of **317**. The oxidative addition of aryl or vinyl halides **318** is followed by an

alkynylation of the adduct **319** to give an aryl or vinyl-alkynyl derivative of palladium

320. The bis(triphenylphosphine)palladium (0) **316** is then regenerated by the reductive

elimination of the substitution products.

$$(PPh_3)_2PdCl_2$$

$$HC\equiv CR$$

$$Cu^I \text{ cat / } Et_2NH$$

$$[NEt_2H_2]Cl$$

$$(Ph_3P)_2Pd\left(C\equiv CR\right)_2$$
315

317

$$RC\equiv\!\!\!\equiv CR$$

R'X

318

'RC≡CR

$$(Ph_3)P\diagdown Pd \diagdown (Ph_3)P\diagup$$
316

$$(Ph_3)P\diagdown\underset{Pd}{}\diagup R' \\ (Ph_3)P\diagup$$
320

R

$$(Ph_3)P\diagdown\underset{Pd}{}\diagup R' \\ (Ph_3)P\diagup X$$
319

$$Cu^I \text{ / } Et_2NH$$

[NEt$_2$H$_2$]Cl   HC≡CR
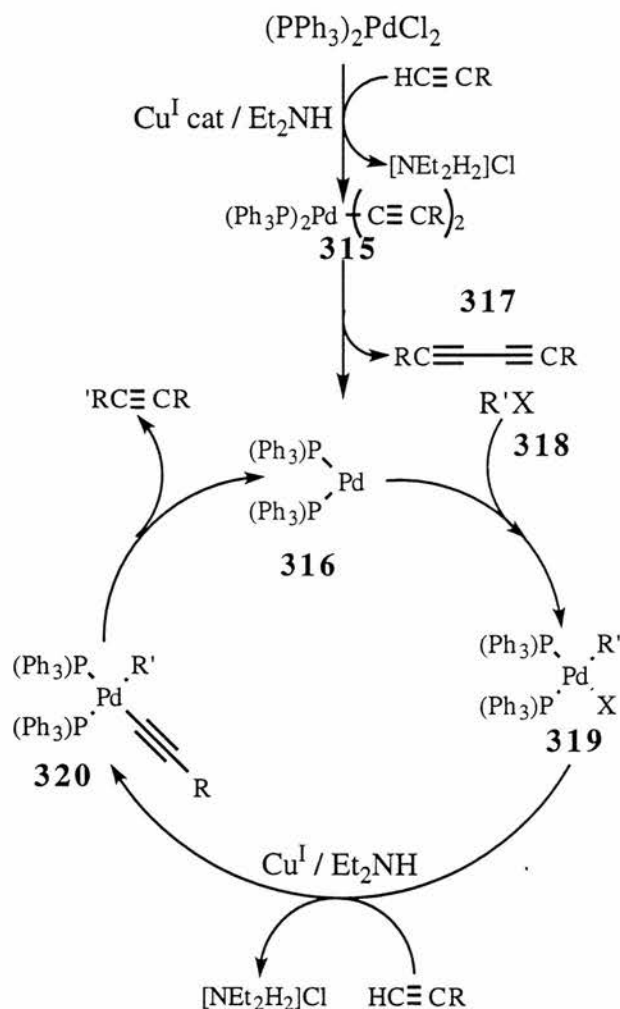
When **306** was reacted as described no bis-*o*-ethynylphenol was formed.

Column chromatography of the reaction mixture gave two fractions, one of which was

starting material **306** and the other corresponded to **317** when R=Ph, i.e. 1,4-

diphenylbutadiyne.[175] This proved that the active catalyst was being produced,

however, the bromobisphenol A was not reactive enough to couple with the catalyst.

Increases in reaction time, reaction temperature, concentration of reactants and solvent

changes were not successful.

The synthesis of iodobisphenol A **321** was attempted as we believed that an iodo compound would be more likely to react under the aforementioned conditions. Conversion of **306** into **321** was attempted using iodine in fuming nitric acid;[176] however no substitution occurred.
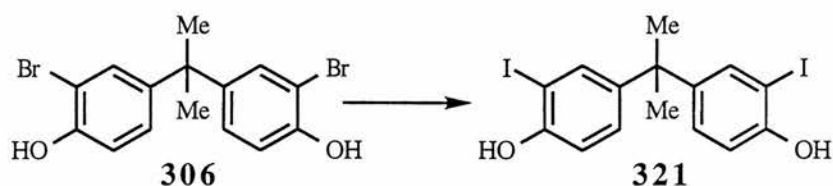
A series of symmetrically substituted alkylated 4,4'-isopropylidenebisphenols have been reported.[177] The method involves passing HCl gas over the phenol and acetone and heating to 60°C for 8 hours and is considered to be a two-step electrophilic substitution.[178] An attempt to form iodobisphenol A **321** from *o*-iodophenol **309** and acetone with a catalytic amount of acid was carried out but was unsuccessful, giving (by tlc) starting material and a highly polar material, possibly a polymer.
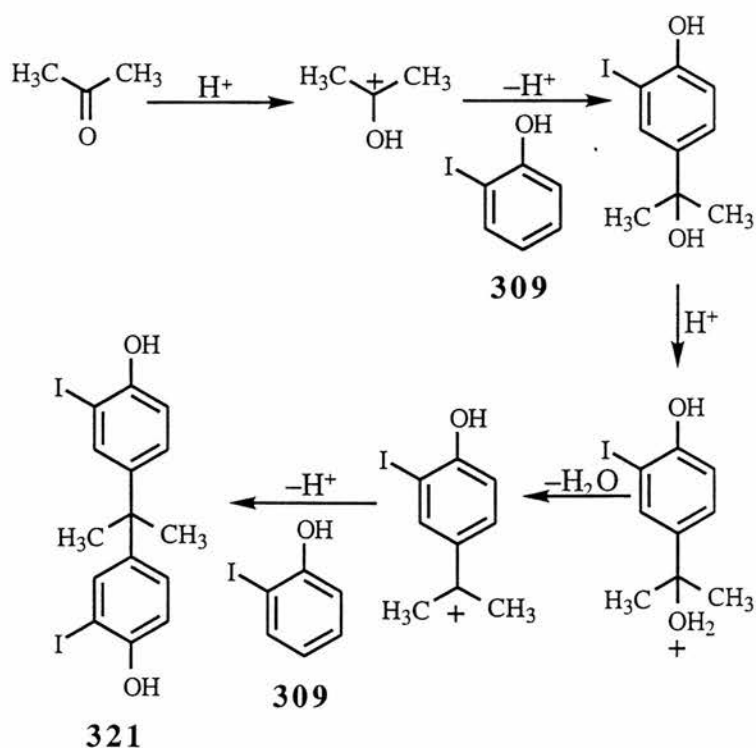
An alternative route to bis *o*-ethynylphenols was thus sought. It was considered that bis-*o*-ethynylphenol **322** could be synthesised by treatment of biphenol **323** with acetic anhydride to give **324**,[179] followed by a Fries rearrangement in boiling nitrobenzene to give **325**.[180] The Fries rearrangement required such high temperatures as lower reaction temperatures resulted only in the regeneration of biphenol. Previously reported Fries rearrangements suggest that *o*-and *p*-acylphenols can be produced, high temperatures favouring *ortho* products, however, the reaction sequence described in our case has the *para*-position protected and therefore no complications of such a nature are observed. The formation of **322** can then be achieved by the successive action of phosphorus pentachloride and sodamide using a literature procedure[170] established for the synthesis of binuclear acetylenic phenols. However, only a 5% yield of the correct material was obtained. Alternative methods must be sought to improve the yield of this final step, so that studies of the intramolecular Diels-Alder reaction with bis-1,2,4-triazines can be attempted.
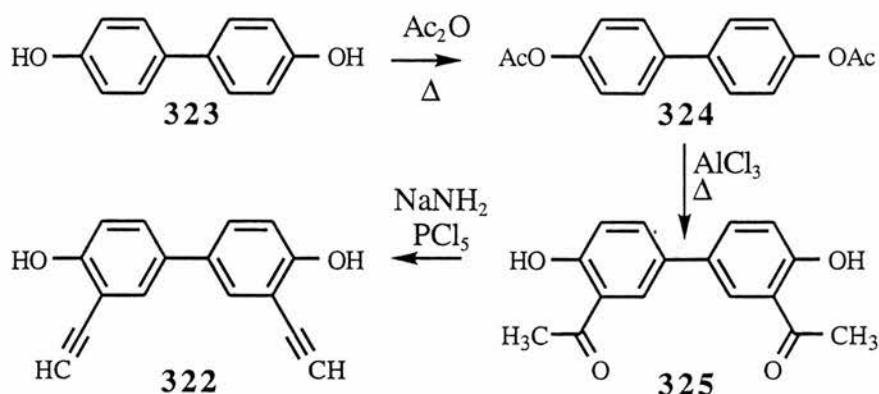
Another member of the research group had attempted to form **326** by the literature method of *Kotlyarevskii et al* [181] shown below. Bisphenol A **255** when treated with sodium hydroxide and iodomethane resulted in the formation of **327**. A Friedel-Crafts reaction gave **328**, methylation gave **329** and finally reduction in the presence of phosphorus pentachloride and sodamide gave 2,2-bis-(3-ethynyl-4-methoxyphenyl)propane **326**. However, the conversion of **327** to **328** by a Friedel

Crafts reaction by the other member of the group gave mixtures of products and the route was abandoned.

326

255   **327**

329   **328**
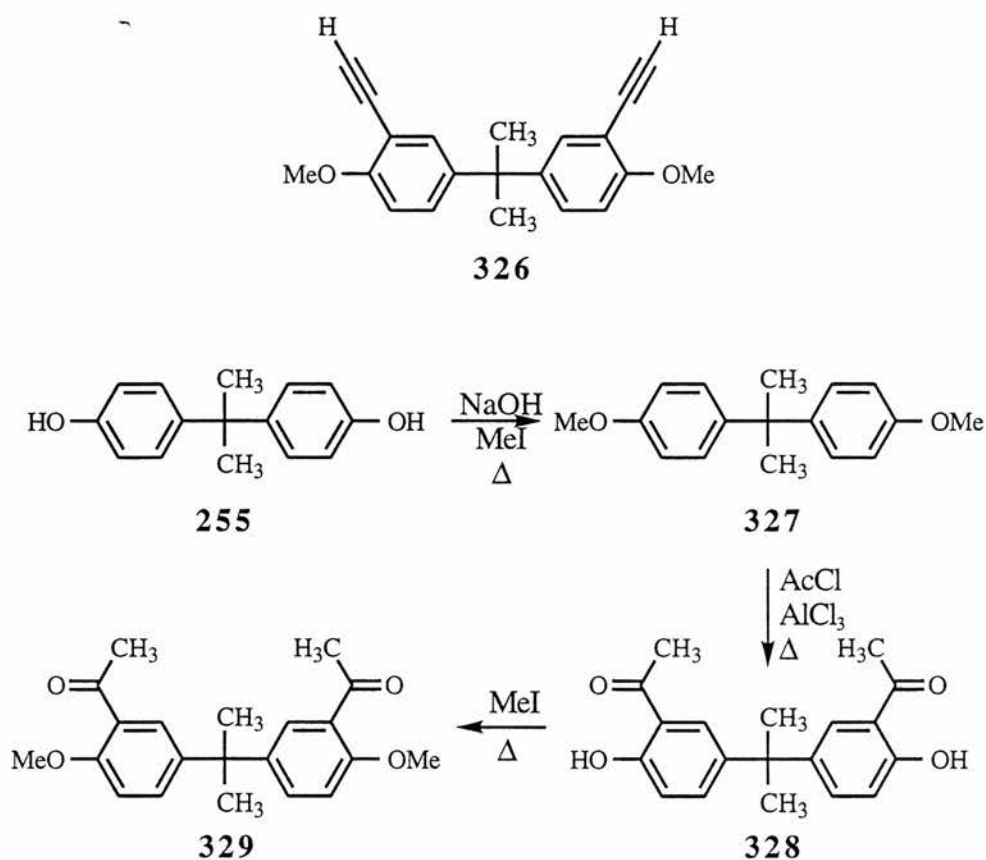
It was decided that **326** would be better synthesised by the method previously developed for the synthesis of **322**.

255   **330**

328
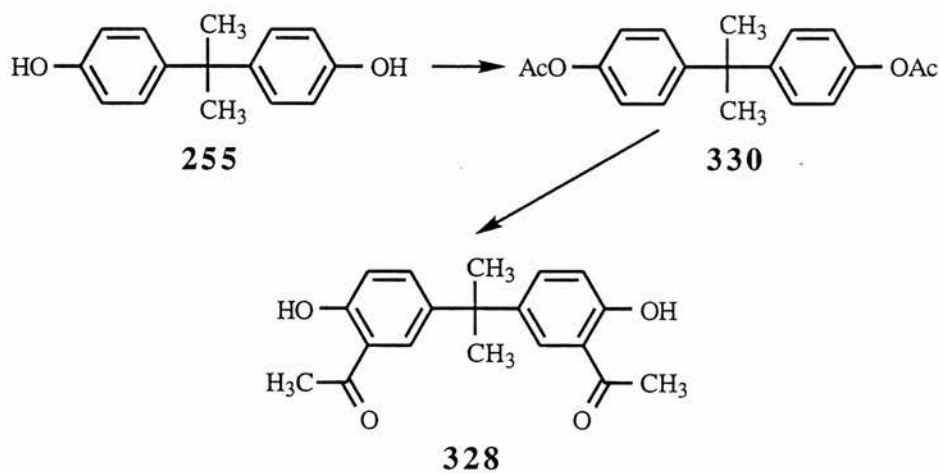
4,4'-isopropylidenebis(phenyl) diacetate **330**[182] was synthesised from bisphenol A and acetic anhydride and an attempt at the Fries rearrangement to give **328**[183] was only partly successful and gave an oil which did not solidify and was shown to be starting material and product in the ratio 3:1 respectively. Attempts at separation of the mixture by column chromatography were unsuccessful. Variations in reaction time, solvent and reaction procedures made no significant improvement in the quantity of **328** observed by NMR.

16. Conclusion

The thesis describes synthetic attempts towards the synthesis of novel heteroaromatic polymers which make use of the inverse electron demand Diels-Alder reaction. Two synthetic routes to novel electron-deficient bis-1,2,4-triazines have been established and the routes have been shown to be of a general nature. A variety of bis-dienophiles have also been synthesised. It was considered that the intermolecular inverse electron-demand Diels-Alder reaction of the bis-1,2,4-triazines with bis-dienophiles, with loss of a small volatile molecule from the initial adduct would result in a polymer. Unfortunately, all attempts at such reactions have been unsuccessful. Since a large negative value for activation volume (which gives a measure of the change in volume of reactants in going to the transition state) is observed in Diels-Alder reactions, the reactions can often be favoured by increasing pressure Therefore attempts at an increased pressure may prove successful.

The intramolecular Diels-Alder reaction with bis-*o*-ethynylphenols for example, would however provide the best chance of reaction as the entropy of activation is often greatly reduced for the intramolecular Diels-Alder reaction as the two components are constrained within the same molecule. The synthesis of a bis-*o*-ethynylphenol for use in an intramolecular Diels-Alder reaction attempt was attempted, however the final step was of a very low yield and future work would therefore be required in order to improve this yield. The bis-*o*-ethynylphenol could be tethered to the bis-1,2,4-triazines and may then react in an intramolecular Diels-Alder reaction.

Another member of the research group, Dr. B. Royles has investigated a synthetic route to bis-1,2,4,5-tetrazines. As was described in the Introduction (page 31), 1,2,4,5-tetrazines have been shown to be one of the most reactive dienes for use in the inverse electron demand Diels-Alder reaction.[184,185] This reactivity was also confirmed by the MOPAC calculation results discussed earlier (pages 58–60). It was similarly considered that bis-1,2,4,5-tetrazines would react with bis-dienophiles to give heteroaromatic polymers. Only one other bis-tetrazine **330** is reported in the literature[186] and was obtained only in a 1% yield overall (5 steps).

330
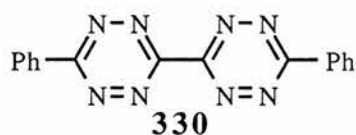
A route to the bis-tetrazines **331** was therefore developed and gives the required compounds in overall reaction yields of at least 40% (3 steps). The reaction sequence for synthesis is shown below.

overall yield ≥ 40%

331
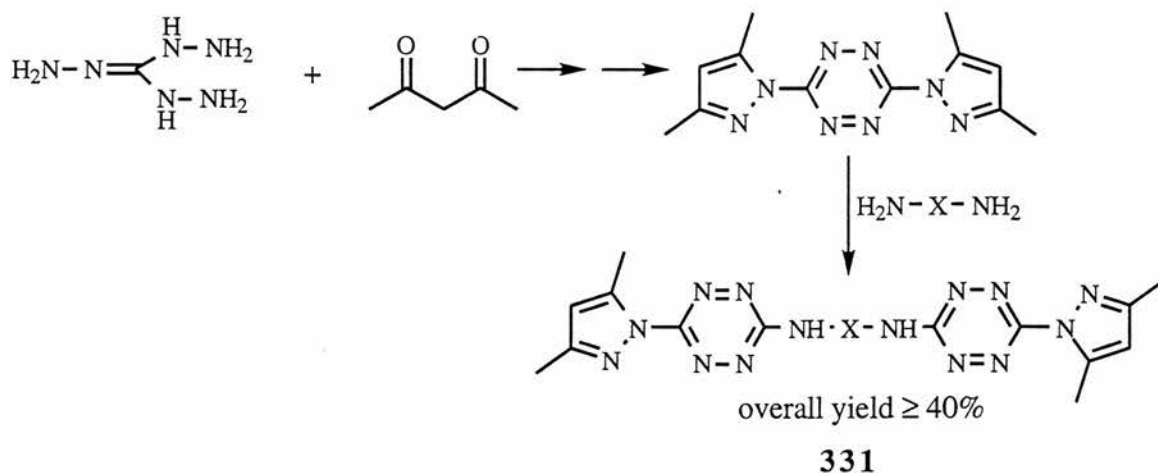
These bis-tetrazines are to be reacted with a variety of bis-dienophiles and will hopefully result in the formation of a polymer, whose properties can then be evaluated with regard to high performance properties. The polymers, being heteroaromatic, will

hopefully have both a high glass transition temperature and melting point. The evaluation of the polymers' properties: molecular weight (by gel permeation chromatography), thermal properties (by differential scanning calorimetry) and mechanical properties (by using impact tests) will then be carried out.

Chapter 3
Experimental

A. Symbols and Abbreviations

mmol	millimoles
M	$mol\ dm^{-3}$
h, min	hours, minutes
tlc	thin layer chromatography
NMR	nuclear magnetic resonance
δ	chemical shift in parts per million
J	spin-spin coupling constant in Hertz
s, d, t, q, m,	singlet, doublet, triplet, quartet, multiplet
bs	broad singlet
ν_{max}	infrared absorption frequency in cm^{-1}
m/z	mass to charge ratio
M^+	mass of molecular ion
m.p.	melting point
b.p.	boiling point
eq.	equivalent
1 mmHg	133.32 Pa
EI	electron impact
CI	chemical ionisation
conc.	concentrated
dec.	decomposition

Instrumentation and General Techniques

1.   N.M.R. spectroscopy

a)   <u>^{1}H NMR</u>

All routine spectra were recorded at 200 MHz on a Varian Gemini 200 instrument by the author while those of new compounds were recorded by Mrs M. Smith on a 300MHz Bruker AM-300 spectrometer.

b)   <u>^{13}C NMR</u>

All routine spectra were recorded by the author on a Varian Gemini 200 instrument operating at 50.3 MHz while spectra of new compounds were recorded by Mrs M. Smith on a Bruker AM-300 running at 75.5 MHz.

All ^{1}H and ^{13}C NMR spectra were obtained from solutions in deuteriochloroform, except where stated that hexadeuteriodimethyl sulphoxide or deuterium oxide were used. Chemical shifts for both ^{1}H and ^{13}C are expressed in parts per million to high frequency of internal tetramethylsilane or, in the case of D_2O solutions internal sodium 3-(trimethylsilyl)-1-propanesulphonate.

2.   Infrared spectroscopy

Spectra were recorded using a Perkin-Elmer 1420 ratio recording spectrophotometer or Perkin-Elmer 1710 Fourier transform spectrophotometer. The spectra were run between sodium chloride plates as a Nujol mull for solids or as a thin film for liquids. The spectra were calibrated with the polystyrene peak at 1603 cm^{-1}.

3.   Mass spectrometry

Mass spectra were obtained on a Fisons VG Autospec mass spectrometer by Mr C. Millar. Unless otherwise stated the spectra were obtained by electron impact.

4.   Elemental analysis

Microanalysis for carbon, hydrogen and nitrogen were carried out by Mrs S. Smith using a Carlo-Erba 1106 elemental analyser.

5.   **Melting points**

Routine melting points were determined on an Electrothermal 9100 melting point machine while accurate melting points of new compounds were determined on a Reichert hot-stage microscope. All melting points are uncorrected.

6.   **Thin layer chromatography**

Aluminium sheets coated with 0.2 mm of silica (Merck, Kieselgel $60F_{254}$) were used and the components observed under ultraviolet light.

7.   **Column chromatography**

This was carried out using Fisons silica gel (60-120 mesh).

8.   **Preparative tlc**

Plates were made by the author using Aldrich tlc grade silica (pore diameter 60 Å)

9.   **Drying and evaporation of organic solutions**

All organic solutions were dried by adding appropriate amounts of anhydrous magnesium sulphate unless otherwise stated. This was filtered off and the filtrate evaporated under reduced pressure on a Büchi rotary evaporator.

10.   **Preparation of anhydrous solvents**

Once dried all solvents were stored over 4Å molecular sieves, stored under nitrogen and the storage vessels sealed.

Methanol

Clean dry magnesium turnings (5.0 g), iodine (0.5 g) and methanol (75 ml, AR grade) were warmed to 40 °C until the iodine had disappeared. The mixture was heated under reflux until all the magnesium disappeared, then methanol (900 ml, AR grade) was added and again heated under reflux for 30 min and then distilled (b.p. 65 °C).

Dioxan

Dioxan (500 ml), concentrated hydrochloric acid (7 ml) and water (50 ml) was heated under reflux for 10 h under nitrogen (to remove the acetaldehyde formed). The solution was cooled and shaken with potassium hydroxide pellets (20 g). The alkaline aqueous layer was separated off and the dioxan stored over potassium hydroxide pellets (20 g) for 24 h. The solvent was decanted and heated under reflux with sodium for 10 h and then distilled from the sodium, b.p. 102 °C at 760 mmHg.

Dichloromethane

Dichloromethane was stored over calcium hydride overnight and then distilled (b.p. 40–41 °C).

Chloroform

The chloroform was passed through a column of basic alumina (10 g per 20 ml of solvent).

Diethyl ether, Tetrahydrofuran, Toluene

Sodium wire was added to analar solvent.

Ethyl acetate

Ethyl acetate (1 l), acetic anhydride (100 ml) and sulphuric acid (5 drops) were heated under reflux for 5 h and fractionated. The distillate was shaken with anhydrous potassium carbonate (20 g), filtered and redistilled (b.p. 77 °C at 760 mmHg).

Nitrobenzene

Nitrobenzene was dried over calcium chloride and then distilled (210 °C at 760 mmHg).

N,N-Dimethylformamide

N,N-Dimethylformamide was stored over calcium hydride overnight and then distilled under reduced pressure (b.p. 76 °C at 40 mmHg).

Triethylamine

Triethylamine was stored over potassium hydroxide pellets and then distilled (b.p. 90 °C).

B. Bis diene synthesis: 5,5'-bis-1,2,4-triazines

1. Construction of 1,2,4-triazine at either 'end' of a core unit

A. Preparation of the diketones: Friedel-Crafts acetylation

A solution of acetyl chloride (10.2 g, 8.9 ml, 130 mmol) in dichloromethane (35 ml) was cooled to 0 °C and aluminium chloride (17.3 g, 130 mmol) was then added, in small portions with stirring over 1 h. A solution of the appropriate diphenyl compound (50 mmol) in dichloromethane (7 ml) was added dropwise over 30 min. The mixture was allowed to warm to room temperature and stirred for 18 h. The solution was then poured slowly into ice/water (100 ml) and the mixture stirred for a further 1 h. The organic layer was separated, the aqueous layer extracted with dichloromethane (3 x 25 ml) and the combined extracts dried, evaporated and recrystallised from ethanol.

Preparation of bis-(4-acetylphenyl) ether 194

The method of B1A was followed using diphenyl ether (8.51 g, 50 mmol) to afford bis-(4-acetylphenyl) ether (10.40 g, 82%) as colourless plates, m.p. 100–101 °C (lit.,[121] 100–101 °C); ν_{max} 1696 cm^{-1} (C=O); δ_H 2.59 (6 H, s, 2 CH$_3$) and 7.06 and 7.98 (8 H, AA'BB', Ar-H).

Preparation of 4,4'-diacetylbiphenyl 195

The method of B1A was followed using biphenyl (7.71 g, 50 mmol) to afford 4,4'-diacetylbiphenyl (7.62 g, 64%) as colourless plates, m.p. 189–190 °C (lit.,[122] 191 °C); ν_{max} 1696 cm^{-1} (C=O); δ_H 2.64 (6 H, s, 2 CH$_3$) and 7.71 and 8.02 (8 H, AA'BB', Ar-H).

Preparation of bis-(4-acetylphenyl) sulphide 196

The method of B1A was followed using diphenyl sulphide (9.30 g, 50 mmol) to afford bis-(4-acetylphenyl) sulphide (13.23 g, 98%) as colourless plates, m.p. 86–87 °C (lit.,[123] 90–91 °C); ν_{max} 1698 cm^{-1} (C=O); δ_H 2.60 (6 H, s, 2 CH$_3$) and

7.38 and 7.90 (8 H, AA'BB', Ar-H).

Preparation of bis-(4-acetylphenyl) sulphoxide **204**

Bis-(4-acetylphenyl) sulphide (6.75 g, 25 mmol) was added portionwise to a solution of magnesium monoperoxyphthalate (15.5 g, 25 mmol) in acetic acid (50 ml). Heat was evolved and a colourless precipitate formed after 10 min. The reaction mixture was then stirred for 12 h, added to water (400 ml) and stirred at room temperature for 10 min. The solid was filtered and recrystallised from acetic acid/water (1:1) to afford bis-(4-acetylphenyl) sulphoxide (3.58 g, 50%) as colourless needles. The analytical sample was further recrystallised thrice from toluene to obtain colourless needles, m.p. 168–170 °C (Found: C, 66.0; H, 4,6. $C_{16}H_{14}O_3S$ requires C, 67.1; H, 4.9%)*; v_{max} 1030 (SO) and 1698 cm^{-1} (C=O); δ_H (CD$_3$SOCD$_3$) 2.60 (6 H, s, 2 CH$_3$) and 8.00 (8 H, s, Ar-H); δ_C (CD$_3$SOCD$_3$) 27.2 (2 CH$_3$), 129.6 (4 CH, C-3,5), 130.7 (4 CH, C-2,6), 139.1 (2 4^{ry}, C-4), 144.1 (2 4^{ry}, C-1) and 197.6 (2 4^{ry}, C=O). * contamination present, probably bis-(4-acetylphenyl) sulphone. This compound has been reported before,[127] however no data for the compound was given.

Preparation of bis-(4-acetylphenyl) sulphone **205**

Bis-(4-acetylphenyl) sulphide (6.75 g, 25 mmol) was added portionwise to a solution of magnesium monoperoxyphthalate (30.9 g, 50 mmol) in acetic acid (100 ml). Heat was evolved and a colourless precipitate formed after 10 min. The reaction mixture was then stirred for 12 h, added to water (400 ml) and stirred at room temperature for 30 min. The solid was then filtered and recrystallised from acetic acid/water (1:1) to afford bis-(4-acetylphenyl) sulphone (5.29 g, 70%) as colourless needles, m.p. 209–211 °C (lit.,[126] 209 °C); v_{max} 1160 (SO$_2$), 1320 and 1698 cm^{-1} (C=O); δ_H (CD$_3$SOCD$_3$) 2.62 (6 H, s, 2 CH$_3$) and 8.02 (8 H, s, Ar-H); δ_C (CD$_3$SOCD$_3$) 27.3 (2 CH$_3$), 128.3 (4 CH, C-3,5), 129.7 (4 CH, C-2,6), 141.0 (2 4^{ry}, C-1), 144.0 (2 4^{ry}, C-4) and 197.7 (2 4^{ry}, C=O).

Attempted preparation of 2,8-diacetyldibenzofuran **200**

The method of B1A was followed using dibenzofuran and shown to consist of a mixture of the monoacetyl and diacetyl compounds (by ^{1}H NMR).

Preparation of 2,8-diacetyldibenzofuran **200**

A solution of acetyl chloride (10.20 g, 8.9 ml, 130 mmol) in 1,2-dichloroethane (50 ml) was stirred and aluminium chloride (17.31 g, 130 mmol) was then added, in small portions with stirring, over 1 h. A solution of dibenzofuran (8.40 g, 50 mmol) in 1,2-dichloroethane (50 ml) was added dropwise, with warming to 50 °C during 30 min. The mixture was heated under reflux for 12 h, cooled to 30 °C, poured slowly into ice/water (100 ml) containing concentrated hydrochloric acid (20 ml) and the mixture stirred for a further 1 h. The organic layer was separated, the aqueous layer extracted with dichloromethane (3 x 25 ml) and the combined extracts dried, evaporated and the cream powder recrystallised from ethanol (with charcoal) to afford 2,8-diacetyldibenzofuran (11.34 g, 90%) as cream needles, m.p. 157–158 °C (lit.,[124] 160 °C); v_{max} 1696 cm^{-1} (C=O); δ_H 2.61 (6 H, s, 2 CH$_3$), 6.65 (2 H, d, J 9, H-4,6), 7.18 (2 H, dd, J 9, 2, H-3,7) and 7.62 (2 H, d, J 2, H-1,9); m/z 252 (M$^+$, 61%), 237 (100), 209 (11), 194 (65), 166 (22), 138 (25) and 111 (20).

Preparation of 2,8-diacetyldibenzothiophene **201**

A solution of acetyl chloride (10.20 g, 8.9 ml, 130 mmol) in 1,2-dichloroethane (80 ml) was stirred and aluminium chloride (17.31 g, 130 mmol) was then added, in small portions with stirring, over 1 h. A solution of dibenzothiophene (9.20 g, 50 mmol) in 1,2-dichloroethane (40 ml) was added dropwise, with magnetic stirring during 30 min. The mixture was heated under reflux with stirring for 16 h, cooled to 30 °C, poured slowly in to ice/water (120 ml) containing concentrated hydrochloric acid (20 ml) and the mixture stirred for a further 1 h. The organic layer was separated, the aqueous layer extracted with dichloromethane (3 x 75 ml) and the combined extracts dried, evaporated and recrystallised from ethanol (with charcoal) to afford 2,8-

diacetyldibenzothiophene (8.31 g, 62%) as cream needles, m.p. 205–207 °C (lit.,[125] 208–209 °C); v_{max} 1698 cm^{-1} (C=O); δ_H 2.65 (6 H, s, 2 CH$_3$), 7.44 (2 H, d, J 8, H-4,6), 8.01 (2 H, dd, J 8, 2, H-3,7) and 8.20 (2 H, d, J 2, H-1,9).

Diacetylbenzene was commercially available and used without further purification.

B. Preparation of the bis-glyoxals

Hydrogen bromide (aqueous 48%, 17 ml, 150 mmol) was added dropwise with stirring over a period of 20 min to a solution of the bis-acetyl compound (25 mmol) in dimethyl sulphoxide (80 ml) (N.B. Dimethyl sulphide is produced!). The temperature is increased to 60 °C and stirring continued at this temperature for 18 h. The yellow solution was allowed to cool to room temperature and then poured into ice/water (600 ml). If the product obtained at this stage was a pale yellow solid (**15**, **210**, **211** and **212**), it was filtered off, washed with water (30 ml) then sucked dry.

In cases where no precipitation occurred (i.e. **207**, **208** and **209**) the aqueous mixture was extracted with ethyl acetate (3 x 200 ml) and the combined extracts washed with sodium thiosulphate solution (10%, 300 ml), then with water (100 ml) then dried. Removal of the solvent afforded the required bis-glyoxal as a pale-yellow solid.

The bis-glyoxals were recrystallised from dioxan/water (1:2) to afford the required compound as hydrates (or partial hydrates) and were dried over conc. sulphuric acid under vacuum.

Preparation of 4,4'-oxybis(phenylglyoxal) 15

The method of B1B was followed using bis-(4-acetylphenyl) ether (6.35 g, 25 mmol) to afford 4,4'-oxybis(phenylglyoxal) (4.69 g, 59%) as pale yellow prisms, m.p. 141–144 °C (lit.,[9] 141–143 °C); v_{max} 1599 (aromatic C=C) and 1686 cm^{-1} (aromatic ketone); δ_H (CD$_3$SOCD$_3$) 5.71 (2 H, s, C$\underline{H}$(OH)$_2$), 6.20 (4 H, bs, OH) and 7.15 and 8.17 (8 H, AA'BB', Ar-H); δ_C (CD$_3$SOCD$_3$) 89.7 (2 CH(OH)$_2$), 119.1

(4 CH, C-2,6), 130.0 (4 CH, C-3,5), 132.7 (2 4^{ry}, C-4), 160.1 (2 4^{ry}, C-1) and 195.4 (2 4^{ry}, C=O); m/z 282 (M$^+$, 1%), 269 (40), 253 (100), 241 (24), 225 (27), 196 (62), 168 (14), 139 (29) and 121 (6).

Preparation of 4,4'-bis(phenylglyoxal) 210

The method of B1B was followed using 4,4'-diacetylbiphenyl (5.95 g, 25 mmol) to afford 4,4'-bis(phenylglyoxal) (6.87 g, 91%) as a pale yellow powder, m.p. 154–157 °C (dec.) (lit.,[117] 150 °C); ν_{max} 1599 (aromatic C=C) and 1686 cm^{-1} (aromatic ketone); δ_H (CD$_3$SOCD$_3$) 5.74 (2 H, s, CH(OH)$_2$), 6.84 (4 H, bs, OH) and 7.92 and 8.20 (8 H, AA'BB', Ar-H); δ_C (CD$_3$SOCD$_3$) 89.8 (2 CH(OH)$_2$), 126.8 (4 CH, C-2,6), 129.6 (4 CH, C-3,5), 135.1 (2 4^{ry}, C-4), 143.9 (2 4^{ry}, C-1) and 195.6 (2 4^{ry}, C=O); m/z 266 (M$^+$, 1%), 237 (100), 209 (7), 180 (72), 152 (40), 126 (15), 104 (17) and 90 (12).

Preparation of 2,8-diglyoxalyldibenzofuran 212

The method of B1B was followed using 2,8-diacetyldibenzofuran (6.30 g, 25 mmol) to afford 2,8-diglyoxalyldibenzofuran (6.64 g, 84%) as a white powder, m.p. 133–135 °C (Found: C, 60.7; H, 3.5. C$_{16}$H$_8$O$_5$.2H$_2$O requires C, 60.8; H, 3.8%); ν_{max} 1599 (aromatic C=C) and 1686 cm^{-1} (aromatic ketone); δ_H (CD$_3$SOCD$_3$) 5.86 (2 H, s, CH(OH)$_2$), 6.82 (4 H, bs, OH), 7.89 (2 H, d, J 9, H-4,6), 8.35 (2 H, dd, J 9, 2, H-3,7) and 9.01 (2 H, d, J 2, H-1,9); δ_C (CD$_3$SOCD$_3$) 89.0 (2 CH(OH)$_2$), 111.9 (2 CH, C-4,6), 123.3 (2 4^{ry}, C-9a,9b), 123.5 (2 CH, C-1,9), 129.6 (2 4^{ry}, C-2,8) 129.8 (2 CH, C-3,7), 158.7 (2 4^{ry}, C-4a,5a) and 195.3 (2 4^{ry}, C=O); m/z 316 (M$^+$ + 2H$_2$O, 8%), 280 (4), 251 (100), 223 (57), 194 (84), 166 (24), 138 (36) and 97 (72).

Preparation of 2,8-diglyoxalyldibenzothiophene 211

The method of B1B was followed using 2,8-diacetyldibenzothiophene (6.70 g, 25 mmol) to afford 2,8-diglyoxalyldibenzothiophene (4.98 g, 60%) as a white powder,

m.p. 85–88 °C (Found: M⁺, 332.0369. $C_{16}H_8O_4S.2H_2O$ requires M, 332.0371); ν_{max} 1599 (aromatic C=C) and 1686 cm⁻¹ (aromatic ketone); δ_H (CD₃SOCD₃) 5.81 (2 H, s, C$\underline{H}$(OH)₂), 6.82 (4 H, bs, OH), 7.54 (2 H, d, J 8, H-4,6), 8.17 (2 H, dd, J 8, 2, H-3,7) and 8.48 (2 H, d, J 2, H-1,9); δ_C (CD₃SOCD₃) 89.2 (2 CH(OH)₂), 119.8 (2 CH, C-4,6), 121.8 (2 4^{ry}, C-9a,9b), 125.3 (2 CH, C-1,9), 128.6 (2 4^{ry}, C-2,8) 129.9 (2 CH, C-3,7), 147.3 (2 4^{ry}, C-4a,5a) and 196.0 (2 4^{ry}, C=O); m/z 332 (M⁺ + 2H₂O, 0.5%), 257 (6), 241 (100), 229 (11), 211 (22), 185 (7), 138 (5) and 91 (1).

Preparation of 4,4'-sulphinylbis(phenylglyoxal) 208

The method of B1B was followed using bis-(4-acetylphenyl) sulphoxide (7.15 g, 25 mmol) to afford 4,4'-sulphinylbis(phenylglyoxal) (5.34 g, 61%) as a pale yellow foam*, m.p. 92–98 °C (Found: M⁺, 350.0476. $C_{16}H_{10}O_5S. 2H_2O$ requires M, 350.0477); ν_{max} 1030 (SO), 1600 (aromatic C=C) and 1685 cm⁻¹ (aromatic ketone); δ_H (CD₃SOCD₃) 3.55 (4 H, bs, OH), 5.70 (2 H, s, C$\underline{H}$(OH)₂) and 8.10 and 8.21 (8 H, AA'BB', Ar-H); δ_C (CD₃SOCD₃) 89.6 (2 CH(OH)₂), 130.5 (4 CH, C-2,6), 130.7 (4 CH, C-3,5), 140.1 (2 4^{ry}, C-4), 143.8 (2 4^{ry}, C-1) and 195.5 (2 4^{ry}, C=O); m/z 350 (M⁺ + 2H₂O, 3%), 314 (7), 299 (100), 287 (31), 271 (56), 243 (20), 157 (16) and 95 (12).

* contamination with trace of 4,4'-sulphonylbis(phenylglyoxal)

Preparation of 4,4'-sulphonylbis(phenylglyoxal) 207

The method of B1B was followed using bis-(4-acetylphenyl) sulphone (7.55 g, 25 mmol) to afford 4,4'-sulphonylbis(phenylglyoxal) (6.04 g, 66%) as a pale yellow powder, m.p. 135–136 °C (lit.,[128] 138–139 °C); ν_{max} 1155, 1321 (SO₂), 1599 (aromatic C=C) and 1686 cm⁻¹ (aromatic ketone); δ_H (CD₃SOCD₃) 3.50 (4 H, bs, OH), 5.68 (2 H, s, C$\underline{H}$(OH)₂) and 8.08 and 8.15 (8 H, AA'BB', Ar-H); δ_C (CD₃SOCD₃) 89.5 (2 CH(OH)₂), 128.3 (4 CH, C-2,6), 130.1 (4 CH, C-3,5), 140.1 (2 4^{ry}, C-4), 145.1 (2 4^{ry}, C-1) and 195.8 (C=O); m/z 366 (M⁺ + 2H₂O, 6%), 331 (8), 317 (14), 301 (36), 289 (58), 273 (44), 244 (14), 216 (11), 169 (68), 121 (46)

and 104 (100).

Preparation of 1,4-di(glyoxal-2-yl)benzene **209**

The method of B1B was followed using 1,4-diacetylbenzene (4.05 g, 25 mmol) to afford 1,4-di(glyoxal-2-yl)benzene (1.02 g, 18%) as colourless prisms, m.p. 150–156 °C (lit.,[88] 160–162 °C); v_{max} 1599 (aromatic C=C) and 1686 cm^{-1} (aromatic ketone); δ_H (CD$_3$SOCD$_3$) 3.60 (4 H, bs, OH), 5.71 (2 H, s, CH(OH)$_2$) and 8.28 (4 H, s); δ_C (CD$_3$SOCD$_3$) 89.6 (2 CH(OH)$_2$), 128.7 (4 CH), 138.4 (2 4^{ry}, C-1,4) and 195.7 (2 4^{ry}, C=O); m/z 190 (M$^+$, 35%), 177 (100), 149 (72), 133 (67), 121 (32), 104 (96) and 89 (21).

Attempted preparation of the bis-glyoxals **15** and **210**

Hydrogen bromide (aqueous 48%, 17 ml, 150 mmol) was added dropwise with stirring over a period of 20 min to a solution of the bis-acetyl compounds (25 mmol) in dimethyl sulphoxide (80 ml) (N.B. dimethyl sulphide is produced!). The temperature was increased to 80 °C and stirring continued at this temperature for 5 h. The yellow solutions were allowed to cool to room temperature and then poured into ice/water (600 ml). Black oils formed at the bottom of the flask and were extracted with ethyl acetate (3 x 50 ml) and shown to consist of the required bis-glyoxals and a complex mixture of products (as shown by ^{1}H NMR and tlc) which were unidentified.

Preparation of *S*-methylthiosemicarbazidium iodide **148**

A solution of thiosemicarbazide (9.10 g, 100 mmol) and iodomethane (14.21 g, 100 mmol) was heated under reflux in ethanol (100 ml) for 90 min, cooled and the solid which precipitated was filtered and recrystallised from ethanol to afford *S*-methylthiosemicarbazidium iodide (20.27 g, 87%) as colourless needles, m.p. 134–136 °C (lit.,[98] 136 °C); δ_H (D$_2$O) 2.61 (3 H, s); δ_C (D$_2$O) 13.5 (CH$_3$) and 167.5 (4^{ry}).

C. Preparation of bis-1,2,4-triazines

A solution of *S*-methylthiosemicarbazidium iodide (2.33 g, 10 mmol) in the minimum volume of aqueous ethanol (15 ml, 50%) was added to a solution of the bis-glyoxal (5 mmol) and sodium bicarbonate (0.93 g, 11 mmol) in aqueous ethanol (50%, 30 ml). The mixture (in which a yellow colour was seen almost immediately) was stirred at room temperature for 48 h. The orange-yellow suspension was then extracted with dichloromethane (3 x 100 ml), the extracts combined, washed with water (100 ml), dried and evaporated to give an orange solid-foam. Preparative tlc (ether:petrol (1:1)) followed by recrystallisation from ethyl acetate/toluene mixtures or ethanol afforded the required bis-1,2,4-triazines as yellow solids.

Notes:

- Attempted reactions in water as solvent gave reduced yields, particularly when the bis-glyoxal was insoluble in water.

- The use of purified glyoxals and heating the reaction mixture under reflux in ethanol gave no significant improvement in yield, however the purification of the bis-triazine was made easier by the use of purified glyoxals.

- Attempts at column chromatography (ether:petrol 40/60 1:1) of the crude bis-1,2,4-triazines gave 'streaking' on column and was therefore abandoned.

Preparation of 3,3'-di(methylsulphanyl)-5,5'-(oxydi-*p*-phenylene)di-1,2,4-triazine 215

The method of B1C was followed using 4,4'-oxybis(phenylglyoxal) (1.59 g, 5 mmol) to afford 3,3'-di(methylsulphanyl)-5,5'-(oxydi-*p*-phenylene)di-1,2,4-triazine (0.65 g, 31%) as a yellow powder which was recrystallised from ethanol to give yellow needles, m.p. 186.5–188 °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%); v_{max} 780, 1240, 1540 and 1600 cm^{-1}; δ_H 2.72 (6 H, s, 2 CH$_3$), 7.21 (4 H, d, *J* 8, H-3,5), 8.22 (4 H, d, *J* 8, H-2,6) and 9.38 (2 H, s, H-6'); δ_C 13.9 (2 CH$_3$), 119.8 (4 CH, C-2,6), 128.8 (4 CH, C-3,5), 129.9 (2 4^{ry}, C-4), 141.6 (2 CH, C-6'), 153.6 (2 4^{ry}, C-5'), 160.0 (2 4^{ry}, C-1) and 173.7 (2 4^{ry}, C-3'); *m/z* 420 (M$^+$, 25%), 319 (15), 218 (100), 189 (15) and 101 (23).

Preparation of 3,3'-di(methylsulphanyl)-5,5'-(di-*p*-phenylene)di-1,2,4-triazine **216**

The method of B1C was followed using 4,4'-bis(phenylglyoxal) (1.51 g, 5 mmol) to afford 3,3'-di(methylsulphanyl)-5,5'-(di-*p*-phenylene)di-1,2,4-triazine (0.48 g, 24%) as a yellow foam which was recrystallised from ethyl acetate:toluene (4:1) to give yellow needles, m.p. 243–245 °C (Found: C, 59.3; H, 3.9; N, 20.6. $C_{20}H_{16}N_6S_2$ requires C, 59.4; H, 4.0; N, 20.8%); v_{max} 780, 1240, 1540 and 1600 cm⁻¹; δ_H 2.74 (6 H, s, 2 CH₃), 7.85 (4 H, d, *J* 8, H-3,5), 8.28 (4 H, d, *J* 8, H-2,6) and 9.41 (2 H, s, H-6'); δ_C 14.0 (2 CH₃), 126.9 (4 CH, C-2,6), 128.0 (4 CH, C-3,5), 133.0 (2 4ry, C-4), 141.8 (2 CH, C-6'), 143.8 (2 4ry, C-1), 153.9 (2 4ry, C-5') and 173.9 (2 4ry, C-3'); *m/z* 404 (M⁺, 12%), 361 (1), 303 (6), 202 (49), 178 (100), 152 (8) and 126 (3).

Preparation of 2,8-bis-3-(methylsulphanyl-1,2,4-triazin-5-yl)dibenzofuran **218**

The method of B1C was followed using 2,8-diglyoxalyldibenzofuran (1.58 g, 5 mmol) to afford 2,8-bis-3-(methylsulphanyl-1,2,4-triazin-5-yl)dibenzofuran (0.84 g, 40%) as a yellow powder which was recrystallised from ethyl acetate:toluene (1:2) to give yellow needles, m.p. 289–291 °C (Found: C, 57.1; H, 3.3; N, 19.8. $C_{20}H_{14}N_6OS_2$ requires C, 57.4; H, 3.4; N, 20.1%); v_{max} 780, 1240, 1540 and 1600 cm⁻¹; δ_H 2.80 (6 H, s, 2 CH₃), 7.79 (2 H, d, *J* 9, H-4,6), 8.35 (2 H, dd, *J* 9, 2, H-3,7), 8.92 (2 H, d, *J* 2, H-1,9) and 9.53 (2 H, s, H-6'); δ_C 14.0 (2 CH₃), 113.1 (2 CH, C-4,6), 121.1 (2 CH, C-1,9), 124.8 (2 4ry, C-9a,9b), 127.8 (2 CH, C-3,7), 128.9 (2 4ry, C-2,8), 141.9 (2 CH, C-6'), 154.1 (2 4ry, C-5'), 159.4 (2 4ry, C-4a,5a) and 173.8 (2 4ry, C-3'); *m/z* 418 (M⁺, 3%), 292 (5), 277 (31), 216 (11), 180 (10), 107 (16) and 91 (100).

Preparation of 2,8-bis-3-(methylsulphanyl-1,2,4-triazin-5-yl)dibenzothiophene **217**

The method of B1C was followed using 2,8-diglyoxalyldibenzothiophene (1.66 g, 5 mmol) to afford 2,8-bis-3-(methylsulphanyl-1,2,4-triazin-5-

yl)dibenzothiophene (0.69 g, 32%) as a yellow powder which was recrystallised from ethanol:ethyl acetate (3:1) to give yellow needles, m.p. 170–172 °C (Found: M+, 434.0431. $C_{20}H_{14}N_6S_3$ requires M, 434.0442)*; ν_{max} 780, 1089, 1240, 1540 and 1600 cm^{-1}; δ_H 2.70 (6 H, s, 2 CH$_3$), 7.51 (2 H, d, J 8, H-4,6), 8.01 (2 H, dd, J 8, 2, H-3,7), 8.15 (2 H, d, J 2, H-1,9) and 9.40 (2 H, s, H-6'); δ_C 14.0 (2 CH$_3$), 120.8 (2 CH, C-4,6), 122.0 (2 CH, C-1,9), 124.8 (2 4^{ry}, C-9a,9b), 127.6 (2 CH, C-3,7), 129.3 (2 4^{ry}, C-2,8), 141.9 (2 CH, C-6'), 148.9 (2 4^{ry}, C-4a,5a), 154.4 (2 4^{ry}, C-5') and 173.8 (2 4^{ry}, C-3'); m/z 434 (M+, 22%), 368 (80), 333 (11), 309 (26), 269 (18), 232 (70), 208 (100), 153 (54), 131 (26), 111 (35) and 83 (72).

* not analytically pure, impurity unknown.

Preparation of 3,3'-di(methylsulphanyl)-5,5'-(*p*-phenylene)di-1,2,4-triazine **219**

The method of B1C was followed using 1,4-di(glyoxal-2-yl)benzene (1.13 g, 5 mmol) to afford 3,3'-di(methylsulphanyl)-5,5'-(*p*-phenylene)di-1,2,4-triazine (0.34 g, 21%) as a yellow powder which was recrystallised from ethanol to give yellow needles, m.p. 246–248 °C (dec.) (Found: C, 51.0; H, 3.4; N, 25.2. $C_{14}H_{12}N_6S_2$ requires C, 51.2; H, 3.7; N, 25.6%) (Found: M+, 328.0558. $C_{14}H_{12}N_6S_2$ requires M, 328.0565); ν_{max} 780, 1240, 1540 and 1600 cm^{-1}; δ_H 2.76 (6 H, s, 2 CH$_3$), 8.35 (4 H, s) and 9.46 (2 H, s, H-6'); δ_C 14.0 (2 CH$_3$), 128.5 (4 CH), 137.0 (2 4^{ry}, C-1,4), 141.8 (2 CH, C-6'), 153.2 (2 4^{ry}, C-5') and 174.2 (2 4^{ry}, C-3'); m/z 328 (M+, 20%), 263 (9), 236 (14), 227 (31), 140 (13), 126 (100) and 101 (10).

Preparation of 3,3'-di(methylsulphanyl)-5,5'-(sulphinyl-*p*-phenylene)di-1,2,4-triazine **214**

The method of B1C was followed using 4,4'-sulphinylbis(phenylglyoxal) (1.75 g, 5 mmol) to afford 3,3'-di(methylsulphanyl)-5,5'-(sulphinyl-*p*-phenylene)di-1,2,4-triazine (0.45 g, 20%) as a yellow powder which was recrystallised thrice from ethyl acetate:toluene (4:1) to give yellow needles, m.p. 205–207 °C (Found: M+, 452.0539. $C_{20}H_{16}N_6OS_3$ requires M, 452.0548)†; ν_{max} 780, 1030 (SO), 1242, 1539

and 1599 cm^{-1}; δ_H 2.80 (6 H, s, 2 CH$_3$), 8.18 (4 H, d, J 8, H-2,6), 8.30 (4 H, d, J 8, H-3,5) and 9.39 (2 H, s, H-6'); δ_C 13.9 (2 CH$_3$), 128.5* (4 CH, C-3,5), 128.9* (4 CH, C-2,6), 138.0 (2 4^{ry}, C-4), 141.8 (2 CH, C-6'), 144.2 (2 4^{ry}, C-1), 152.8 (2 4^{ry}, C-5') and 174.3 (2 4^{ry}, C-3'); m/z 452 (M$^+$, 7%), 436 (30), 351 (12), 335 (25), 250 (11), 234 (100) and 101 (24).

* provisional assignments

† microanalysis revealed contamination, probably 3,3'-di(methylsulphanyl)-5,5'-(sulphonyl-p-phenylene)di-1,2,4-triazine **213**. Repeated recrystallisation did not improve the purity.

Preparation of 3,3'-di(methylsulphanyl)-5,5'-(sulphonyl-p-phenylene)di-1,2,4-triazine **213**

The method of B1C was followed using 4,4'-sulphonylbis(phenylglyoxal) (1.83 g, 5 mmol) to afford 3,3'-di(methylsulphanyl)-5,5'-(sulphonyl-p-phenylene)di-1,2,4-triazine (0.61 g, 26%) as a yellow powder which was recrystallised from ethyl acetate:toluene (4:1) to give yellow needles, m.p. 223–224 °C (Found: C, 51.15; H, 3.2; N, 17.6. C$_{20}$H$_{16}$N$_6$O$_2$S$_3$ requires C, 51.3; H, 3.4; N, 17.9%); ν_{max} 780, 1160 (SO$_2$), 1240, 1321 (SO$_2$), 1540 and 1600 cm^{-1}; δ_H 2.73 (6 H, s, 2 CH$_3$), 8.16 (4 H, d, J 8, H-2,6), 8.30 (4 H, d, J 8, H-3,5) and 9.39 (2 H, s, H-6'); δ_C 14.0 (2 CH$_3$), 128.7* (4 CH, C-2,6), 128.8* (4 CH, C-3,5), 138.3 (2 4^{ry}, C-4), 141.7 (2 CH, C-6'), 144.3 (2 4^{ry}, C-5'), 152.5 (2 4^{ry}, C-1) and 174.4 (2 4^{ry}, C-3'); m/z 468 (M$^+$, 21%), 367 (30), 266 (66), 149 (100), 121 (17) and 101 (43).

* provisional assignments

Flash vacuum pyrolysis of 3,3'-di(methylsulphanyl)-5,5'-(oxydi-p-phenylene)di-1,2,4-triazine **215**

The flash vacuum pyrolysis was carried out at a temperature of 750 °C and at 0.02 mmHg using 3,3'-di(methylsulphanyl)-5,5'-(oxydi-p-phenylene)di-1,2,4-triazine (222.5 mg). A black film (70.2 mg) remained in the inlet tube and was insoluble in many

common organic solvents (ethanol, ethyl acetate, dioxan, dichloromethane, dimethyl sulphoxide, ether), had m.p. >350 °C and was unidentified. A colourless liquid was isolated in the trap and shown to be methyl thiocyanate (30.8 mg); b.p. 129–130 °C (lit.,[129] 131 °C); v_{max} 990, 1400, 2180, 2990 and 3015 cm^{-1}; δ_H 2.61 (3 H, s); δ_C 16.3 (CH$_3$) and 113.2 (4^{ry}). A pale yellow powder was isolated in the furnace exit (115.4 mg) and shown to be 4,4'-diethynyldiphenyl ether; m.p. 75–77 °C (lit.,[130] 77–77.5 °C); v_{max} 2102 (alkyne) and 3285 cm^{-1} (CH); δ_H (CD$_3$SOCD$_3$) 3.10 (2 H, alkyne) and 6.95 and 7.52 (8 H, AA'BB'); δ_C 80.5 (2 CH), 83.1 (2 4^{ry}), 117.3 (2 4^{ry}, C-4), 119.1 (2 CH, C-2), 133.9 (2 CH, C-3) and 157.0 (2 4^{ry}, C-1).

D. Preparation of bis-sulphoxides

m-Chloroperbenzoic acid (0.44 g, 2.54 mmol, 2.13 equiv.) was added (in one portion) to a solution of the bismethylsulphanyl-1,2,4-triazine (1.19 mmol) in anhydrous dichloromethane (10 ml) at 0 °C. The reaction mixture was then stirred at room temperature for 12 h. The solvent was then evaporated and the residue stirred in anhydrous ether (10 ml) for 10 min. The resultant pale yellow-white solid was collected by filtration, washed with anhydrous ether (10 ml) and sucked dry at the pump. Purification was effected by column chromatography (silica gel, anhydrous ethyl acetate: anhydrous tetrahydrofuran 10:1) to give the crude sulphoxides as pale yellow solids. Attempts at further purification by recrystallisation (using for example, petroleum 40/60, ethyl acetate and toluene) gave tars and resulted in decomposition of the product. The bis-sulphoxides were usually used immediately after column chromatography to minimise the observed decomposition.

Notes:

- The bis-sulphoxides are unstable, both thermally and on storage (under nitrogen at –20 °C), and are extremely sensitive to moisture.
- The silica gel was dried in the oven (100 °C for at least 3 days) prior to use.

Preparation of 3,3'-di(methylsulphinyl)-5,5'-(oxydi-_p_-phenylene)di-1,2,4-triazine **230**

The method of B1D was followed using 3,3'-di(methylsulphanyl)-5,5'-(oxydi-_p_-phenylene)di-1,2,4-triazine (0.50 g, 1.19 mmol) to afford 3,3'-di(methylsulphinyl)-5,5'-(oxydi-_p_-phenylene)di-1,2,4-triazine (0.28 g, 52%) as a yellow foam, m.p. 108–110 °C (dec.) (Found: M$^+$, 452.0751. $C_{20}H_{16}N_6S_2O_3$ requires M, 452.0758)*; ν_{max} 780, 1018 (SO), 1240, 1540 and 1600 cm^{-1}; δ_H (CD$_3$SOCD$_3$) 3.17 (6 H, s, 2 CH$_3$), 7.28 (4 H, d, J 8, H-3,5), 8.40 (4 H, d, J 8, H-2,6) and 10.28 (2 H, s, H-6'); δ_C (CD$_3$SOCD$_3$) 39.6 (2 CH$_3$), 121.6 (4 CH, C-2,6), 128.0 (4 CH, C-3,5), 130.0 (2 4^{ry}, C-4), 148.9 (2 CH, C-6'), 156.0 (2 4^{ry}, C-5'), 166.1 (2 4^{ry}, C-1) and 173.4 (2 4^{ry}, C-3'); m/z 452 (M$^+$, CI).

* not analytically pure

Preparation of 3,3'-di(methylsulphinyl)-5,5'-(di-_p_-phenylene)di-1,2,4-triazine **229**

The method of B1D was followed using 3,3'-di(methylsulphanyl)-5,5'-(di-_p_-phenylene)di-1,2,4-triazine (0.48 g, 1.19 mmol) to afford 3,3'-di(methylsulphinyl)-5,5'-(di-_p_-phenylene)di-1,2,4-triazine (0.37 g, 72%) as a yellow foam, m.p. 135–137 °C (dec.) (Found: M$^+$, 436.0803. $C_{20}H_{16}N_6S_2O_2$ requires M, 436.0809)*; ν_{max} 780, 1025 (SO), 1240, 1542 and 1600 cm^{-1}; δ_H (CD$_3$SOCD$_3$) 3.16 (6 H, s, 2 CH$_3$), 8.08 (4 H, d, J 8, H-3,5), 8.42 (4 H, d, J 8, H-2,6) and 10.38 (2 H, s, H-6'); δ_C (CD$_3$SOCD$_3$) 39.6 (2 CH$_3$), 128.0 (4 CH, C-2,6), 129.3 (4 CH, C-3,5), 132.3 (2 4^{ry}, C-4), 143.4 (2 4^{ry}, C-1), 148.9 (2 CH, C-6'), 153.8 (2 4^{ry}, C-5') and 173.4 (2 4^{ry}, C-3'); m/z 436 (M$^+$, CI).

* not analytically pure

Mono-1,2,4-triazine model reactions

Preparation of 3-(methylsulphanyl)-5-phenyl-1,2,4-triazine **224**

A solution of phenylglyoxal monohydrate (1.04 g, 6.86 mmol) and sodium bicarbonate (0.58 g, 6.86 mmol) in ice/water (7 ml) was added to a solution of _S_-methylthiosemicarbazidium iodide (1.60 g, 6.86 mmol) in ice/water (10 ml). After the

effervescence had ceased, the mixture was left at 4 °C for 5 h, extracted with dichloromethane (3 x 50 ml), dried and the solvent evaporated to give a yellow solid which was recrystallised from ethanol to afford 3-(methylsulphanyl)-5-phenyl-1,2,4-triazine (1.18 g, 85%) as yellow needles, m.p. 98–100 °C (lit.,[80] 99–100 °C); δ_H 2.69 (3 H, s), 7.53 (3 H, m, H-2,4,6), 8.12 (2 H, dd, J 8, 2, H-3,5) and 9.34 (1 H, s); δ_C 13.8 (CH_3), 127.6 (2 CH), 129.3 (2 CH), 132.6 (CH), 133.0 (4^{ry}, C-1), 141.8 (CH, C-6'), 154.4 (4^{ry}, C-5') and 173.6 (4^{ry}, C-3').

Preparation of 3-methylsulphonyl-5-phenyl-1,2,4-triazine 225

To a stirred solution of 3-(methylsulphanyl)-5-phenyl-1,2,4-triazine (0.48 g, 2.36 mmol) in anhydrous dichloromethane (20 ml) at 0 °C was added, all at once, *m*CPBA (1.03 g, 5.07 mmol, 2.13 eq. max). The resulting mixture was stirred at room temperature for 5 h, concentrated by evaporation and the residual solid was triturated in ether to give a pale yellow powder. Recrystallisation from anhydrous ether afforded 3-methylsulphonyl-5-phenyl-1,2,4-triazine (0.50 g, 90%) as a cream powder, m.p. 145–147 °C (lit.,[66] 146–148 °C); δ_H (CD_3SOCD_3) 3.54 (3 H, s), 7.53–7.73 (3 H, m), 8.28–8.39 (2 H, dd, J 2, 8) and 10.02 (1 H, s); δ_C (CD_3SOCD_3) 39.1 (CH_3), 128.6 (2 CH), 129.8 (2 CH), 131.5 (4^{ry}, C-1), 134.3 (CH), 147.9 (CH, C-6'), 157.6 (4^{ry}, C-5') and 166.9 (4^{ry}, C-3').

Preparation of 3-methoxy-5-phenyl-1,2,4-triazine 226

A solution containing 3-methylsulphonyl-5-phenyl-1,2,4-triazine (0.50 g, 2.13 mmol) and sodium methoxide (0.11 g, 2.13 mmol) was stirred at room temperature for 15 h, the solvent was evaporated and the solid reprecipitated from methanol to afford 3-methoxy-5-phenyl-1,2,4-triazine (0.28 g, 71%) as a white powder, m.p. 75–77 °C (lit.,[80] 77–78 °C); δ_H 4.20 (3 H, s, OCH_3), 7.52–7.58 (3 H, m), 8.14–8.18 (2 H, dd, J 2, 8) and 9.40 (1 H, s).

E. Attempted preparation of the bis-sulphones using mCPBA

When the same procedure was followed as in B1D using 3,3'-di(methylsulphanyl)-5,5'-(oxydi-p-phenylene)di-1,2,4-triazine, except that double the quantity of m-CPBA was used, the product consisted of a mixture of bis-sulphoxides and bis-sulphones (*ca.* 3:1 by ^{1}H NMR). Separation by column chromatography (silica gel, ethyl acetate:tetrahydrofuran 10:1) proved difficult.

F. Preparation of the bis-sulphones using oxone

Wet alumina (containing 10% water by weight, 2 g) and oxone (6 mol. eq.) were stirred at room temperature in anhydrous chloroform (20 ml). A solution of the sulphide (500 mg, 1.19 mmol) in chloroform was then added dropwise with constant stirring to the reaction mixture and heated under reflux until no bis-sulphide remained (tlc: ether-petroleum, 1:1). The reaction mixture was cooled to room temperature; the filtrate and washings combined and the solvent evaporated. The pale yellow solid was purified by column chromatography (silica gel, anhydrous ethyl acetate: anhydrous tetrahydrofuran 10:1) to give the bis-sulphone as a crude powder. Attempts at further purification by recrystallisation using toluene gave tars and resulted in decomposition of the product. The bis-sulphones were used immediately after column chromatography to minimise decomposition problems.

Notes:

- Reaction attempts without alumina proved unsuccessful.
- The bis-sulphones are unstable, both thermally and on storage (under nitrogen at −20 °C), and are extremely sensitive to moisture giving sticky yellow tars.
- The silica gel was dried in the oven (100 °C for at least 3 days) prior to use.

Preparation of 3,3'-di(methylsulphonyl)-5,5'-(oxydi-p-phenylene)di-1,2,4-triazine 227

The method of B1F was followed using 3,3'-di(methylsulphanyl)-5,5'-(oxydi-p-phenylene)di-1,2,4-triazine (0.50 g, 1.19 mmol) with a reaction time of 3 h to afford 3,3'-di(methylsulphonyl)-5,5'-(oxydi-p-phenylene)di-1,2,4-triazine (0.36 g, 62%) as a

white powder, m.p. 208–211 °C (dec.) (Found: M+, 484.0647. $C_{20}H_{16}N_6S_2O_5$ requires M, 484.0659)*; ν_{max} 780, 1003, 1130, 1150 (SO$_2$), 1240, 1300, 1540 and 1600 cm^{-1}; δ_H (CD$_3$SOCD$_3$) 3.66 (6 H, s, 2 CH$_3$), 8.13 (4 H, d, J 8, H-3,5), 8.60 (4 H, d, J 8, H̄-2,6) and 10.47 (2 H, s, H-6'); δ_C (CD$_3$SOCD$_3$) 39.6 (2 CH$_3$), 119.4 (4 CH, C-2,6), 128.7 (4 CH, C-3,5), 128.9 (2 4^{ry}, C-4), 148.7 (2 CH, C-6'), 155.9 (2 4^{ry}, C-5'), 163.6 (2 4^{ry}, C-1) and 166.0 (2 4^{ry}, C-3'); m/z 484 (M+, 11%), 404 (6), 360 (65), 309 (100), 267 (22), 238 (58), 172 (30), 126 (60) and 91 (29).

* not analytically pure

Preparation of 3,3'-di(methylsulphonyl)-5,5'-(di-*p*-phenylene)di-1,2,4-triazine 228

The method of B1F was followed using 3,3'-di(methylsulphanyl)-5,5'-(di-*p*-phenylene)di-1,2,4-triazine (0.48 g, 1.19 mmol) to afford 3,3'-di(methylsulphonyl)-5,5'-(di-*p*-phenylene)di-1,2,4-triazine (0.43 g, 77%) as a yellow powder, m.p. 79–80 °C (dec.)*. Decomposition occurred on attempted purification by column chromatography. ν_{max} 780, 1140, 1160 (SO$_2$), 1240, 1290, 1320 (SO$_2$), 1540 and 1599 cm^{-1}; δ_H (CD$_3$SOCD$_3$) 3.60 (6 H, s, 2 CH$_3$), 8.18 (4 H, d, J 8, H-3,5), 8.32 (4 H, d, J 8, H-2,6) and 10.43 (2 H, s, H-6'); δ_C (CD$_3$SOCD$_3$) 39.6 (2 CH$_3$), 127.3 (4 CH, C-2,6), 127.5 (2 4^{ry}, C-4), 128.1 (4 CH, C-3,5), 143.2 (2 4^{ry}, C-1), 147.8 (2 CH, C-6'), 152.9 (2 4^{ry}, C-5') and 166.1 (2 4^{ry}, C-3').

2. Coupling reactions of preformed mono-triazines to each other or to a central core unit

A. Coupling reactions of mono-1,2,4-triazines to each other

Preparation of 3-(methylsulphanyl)-1,2,4-triazine 115

A solution of 40% glyoxal (10.47 g, 55.1 mmol) and sodium bicarbonate (3.70 g, 44.1 mmol) in ice/water (100 ml) was added with stirring to S-methylthiosemicarbazidium iodide (9.32 g, 40.2 mmol) in ice/water (60 ml). The reaction was left stirring at room temperature for 30 min and then stored at 4 °C for 5 h.

The mixture was extracted with dichloromethane (3 x 50 ml), dried and the solvent evaporated to afford 3-(methylsulphanyl)-1,2,4-triazine (4.24 g, 83%) as yellow plates, m.p. 31–33 °C (lit.,[80] 31–33 °C); δ_H 2.70 (3 H, s), 8.46 (1 H, d, J 7) and 9.00 (1 H, d, J 7); δ_C 14.1 (CH$_3$), 146.0 (CH, C-6), 148.6 (CH, C-5) and 175.2 (4^{ry}, C-3).

Preparation of 3,3'-dimethoxy-5,5'-bi-1,2,4-triazinyl 117

A solution of 3-(methylsulphanyl)-1,2,4-triazine (5.08 g, 40.0 mmol) in ice cold anhydrous methanol (20 ml) was stirred at room temperature and sodium metal (1.20 g) was added to the mixture in 2 portions over 30 min. The reaction mixture was stirred at room temperature for 16 h, saturated with solid carbon dioxide, the solid filtered and washed with methanol (200 ml) and the washings combined with the filtrate. The combined filtrate was evaporated to dryness and the residue extracted with dichloromethane (3 x 40 ml), dried and evaporated and the resultant solid reprecipitated from methanol to afford 3,3'-dimethoxy-5,5'-bi-1,2,4-triazinyl (2.64 g, 60%) as a yellow powder, m.p. 175–177 °C (lit.,[82] 175–176.5 °C); δ_H 4.34 (6 H, s, 2 CH$_3$) and 9.99 (2 H, s, H-6'); δ_C 56.5 (2 CH$_3$), 141.8 (2 CH, C-6), 152.8 (2 4^{ry}, C-5) and 165.5 (2 4^{ry}, C-3); m/z 220 (M$^+$, 100%), 192 (45), 135 (75), 107 (87), 93 (20) and 80 (33).

Attempted preparation of 3,3'-bis(methylsulphanyl)-5,5'-bi-1,2,4-triazinyl 116

A solution of 3-(methylsulphanyl)-1,2,4-triazine (5.08 g, 40 mmol) in ice-cold anhydrous methanol (20 ml) was stirred at room temperature and sodium metal (1.20 g) was added in 2 portions over 30 min. The mixture was stirred at room temperature for 4 h, saturated with solid CO$_2$ and the solid filtered, washed with methanol (200 ml) and the washings combined with the filtrate. The combined filtrate was evaporated to dryness and the residue extracted with dichloromethane (3 x 40 ml), dried and the solvent evaporated. The resultant mixture was purified by fractional recrystallisation from methanol to yield a first crop of yellow needles shown to be 3-methoxy-1,2,4-triazine

(2.0 g, 45%), m.p. 43–45 °C (lit.,[82] 44–46 °C); δ_H 5.15 (3 H, s, OCH$_3$), 8.56 (1 H, d, J 7) and 9.16 (1 H, d, J 7). A second crop was obtained as a yellow powder and was shown by ^{1}H and ^{13}C NMR and mass spectrometry to be a mixture of dimethoxy- and bis(methylsulphanyl) bis-1,2,4-triazines in the ratio 9:1. Attempts to separate these products by fractional recrystallisation (from ethanol) proved difficult.

Note:

- Variations in the reaction conditions used and monitoring the reaction mixture by UV spectroscopy (λ_{max} 219.6, 261.4 and 368.0) showed no appreciable difference in the amount of the dimethylsulphanyl- dimer which could be obtained.

Attempted preparation of 3,3'-bis(methylsulphanyl)-5,5'-bi-1,2,4-triazinyl 116[82]

A solution containing potassium metal (67.6 mg, 1.73 mmol) in liquid ammonia (40 ml) was stirred and 3-methylsulphanyl-1,2,4-triazine (220 mg, 1.73 mmol) was added as a solid to the reaction mixture. The reaction mixture was left overnight to allow excess ammonia to evaporate at room temperature and was then extracted with dichloromethane (3 x 50 ml), washed with water (50 ml) and dried. The solvent was evaporated to give an orange oil which did not solidify and was shown by ^{1}H NMR to be starting material.

Preparation of 3,3'-bis(methylsulphanyl)-5,5'-bi-1,2,4-triazinyl 116

A solution of 3-methylsulphanyl-1,2,4-triazine (220 mg, 1.73 mmol) in water (15 ml) was stirred and heated for 10 min to 40 °C until the solid had completely dissolved. To this warm solution was added excess potassium cyanide as a solid (500 mg, 5 eq). An immediate red precipitate formed and the reaction mixture was continued stirring for 10 min. The solution was then stirred in ether (250 ml) for 15 min and water (25 ml) was added to the stirred solution. The organic layer was separated and the aqueous layer extracted with ether (3 x 50 ml) and the combined extracts washed with water (3 x 20 ml) and dried (over anhydrous sodium sulphate). The solvent was evaporated and the solid reprecipitated from methanol to afford 3,3'-

bis(methylsulphanyl)-5,5'-bi-1,2,4-triazinyl (140 mg, 64%) as a yellow powder, m.p. 169–170 °C (lit.,[81] 168.5–170 °C); δ_H 2.78 (6 H, s, 2 CH$_3$) and 9.94 (2 H, s, H-6'); m/z 252 (M$^+$, 45%), 224 (40), 151 (19), 123 (100) and 108 (10); λ_{max} 219.6 (ϵ 11560), 261.4 (ϵ 22760) and 368.0 (ϵ 3150).

Note:

• All glassware was soaked after use in a concentrated hypochlorite solution overnight

Attempted preparation of 3,3'-bis(methylsulphonyl)-5,5'-bi-1,2,4-triazinyl 231

To a stirred solution of the 3,3'-bis(methylsulphanyl)-5,5'-bi-1,2,4-triazinyl (50 mg, 0.20 mmol) and anhydrous dichloromethane (5 ml) at 0 °C was added mCPBA (0.14 g, 0.80 mmol) and the reaction was continued stirring at room temperature for 24 h. The reaction mixture was then evaporated and the residual solid was stirred in anhydrous ether (10 ml) and filtered. ^{1}H and ^{13}C NMR revealed a mixture of sulphoxide:sulphone in the ratio 1:3.

Preparation of 3,3'-bis(methylsulphonyl)-5,5'-bi-1,2,4-triazinyl 231

To a stirred solution of the 3,3'-bis(methylsulphanyl)-5,5'-bi-1,2,4-triazinyl (50 mg, 0.20 mmol) in acetic acid (10 ml) at 0 °C was added potassium permanganate (90 mg, 0.57 mmol) and the reaction was continued stirring at room temperature for 24 h. After addition of solid sodium metabisulphite (5 g), the reaction mixture was evaporated and the residual solid was stirred in anhydrous ether (5 ml) and filtered. Column chromatography (silica gel, anhydrous ethyl acetate) was carried out to afford 3,3'-bis(methylsulphonyl)-5,5'-bi-1,2,4-triazinyl (58.8 mg, 93%) as a pale yellow powder, m.p. 120–124 °C (Found: M$^+$, 316.0088. C$_8$H$_8$N$_6$O$_4$ requires M, 316.0083); δ_H (CD$_3$SOCD$_3$) 3.65 (6 H, s, 2 CH$_3$) and 10.61 (2 H, s, H-6'); δ_C (CD$_3$SOCD$_3$) 40.2 (2 CH$_3$), 149.4 (2 CH, C-6'), 153.1 (2 4^{ry}, C-5') and 166.0 (2 4^{ry}, C-3'); m/z 316 (M$^+$, 7%), 289 (6), 256 (10), 237 (65), 210 (50), 189 (67), 164 (63), 136 (100) and 104 (64).

B. Coupling reactions to a central core unit

Mono triazine synthesis

Preparation of phenylglyoxal monohydrate 96[112]

A solution of 48% aqueous HBr (17 ml, 150 mmol) was added dropwise to acetophenone (6.05 g, 50 mmol) in dimethyl sulphoxide (85 ml) over a period of 1 h. The solution was stirred at 55 °C for 24 h, poured on to ice (100 g) and extracted with ethyl acetate (3 x 100 ml) and the solvent evaporated to give a yellow oil. On cooling, a solid formed which was filtered and recrystallised from water to afford phenylglyoxal monohydrate (6.76 g, 89%) as colourless plates, m.p. 76–78 °C (lit.,[187] 74–76 °C); ν_{max} 685, 965, 1037, 1113, 1225, 1305, 1596 and 1698 cm^{-1} (C=O); δ_H (D$_2$O) 5.70 (1 H, s), 7.48–7.54 (2 H, dd, J 8, 2, H-2,6), 7.61–7.69 (1 H, t, J 8, H-4) and 8.10–8.20 (2 H, dd, J 8, 2, H-3,5).

Attempted preparation of 5-phenyl-1,2,4-triazin-3-one 235

A solution of phenylglyoxal monohydrate (4.56 g, 30 mmol) in acetic acid (50 ml) was added to a solution of semicarbazide hydrochloride (2.80 g, 30 mmol) in water (7.5 ml). The reaction mixture was heated under reflux for 4 h and then added to ice/water (100 ml). The yellow precipitate was filtered and reprecipitated from acetic acid/water to afford a pale yellow powder, m.p. 212 °C (lit.,[137] 234 °C). The product was shown to be mainly uncyclised semicarbazone (by ^{1}H and ^{13}C NMR), only 10% of the correct material was obtained. Variations in reaction time made no significant improvement to the yield of 5-phenyl-1,2,4-triazin-3-one formed.

Preparation of 5-phenyl-1,2,4-triazin-3-one 235

To a solution of potassium hydroxide (0.3 g) in water (0.8 ml) was added dropwise with stirring a solution of 5-phenyl-3-(methylsulphanyl)-1,2,4-triazine (0.81 g, 4 mmol) in water (0.8 ml) and the reaction mixture was heated to 50–60 °C with stirring for 3 h. The reaction mixture was evaporated to dryness and the residue reprecipitated from methanol. The salt was dissolved in the minimum of water (2 ml),

neutralised by the dropwise addition of acetic acid and the solid filtered. Reprecipitation from ethanol afforded 5-phenyl-1,2,4-triazin-3-one (0.55 g, 80%) as a white powder, m.p. 240 °C (lit.,[138] 240 °C); ν_{max} 632, 722, 774, 1010, 1291, 1311, 1587 and 1656 cm^{-1}; δ_H^- (CD$_3$SOCD$_3$) 7.50–7.70 (3 H, m, H-2,4,6), 8.22 (2 H, d, J 8, 2, H-3,5) and 8.70 (1 H, s); δ_C (CD$_3$SOCD$_3$) 128.3 (2 CH), 129.1 (2 CH), 131.0 (CH), 133.0 (CH, C-6'), 133.3 (4^{ry}, C-1), 153.9 (4^{ry}, C-5') and 164.4 (4^{ry}, C-3').

Attempted preparation of 3-chloro-5-phenyl-1,2,4-triazine **234**

A solution of 5-phenyl-1,2,4-triazin-3-one (0.87 g, 5.03 mmol) and phosphoryl chloride (5 ml) was heated under reflux for 30 min at 120 °C. The brown solution was evaporated and then poured on to ice (25 g). The brown solid was filtered and washed with 2M ammonia (5 ml) then water (5 ml) and dried (over anhydrous calcium chloride). Attempted purification by column chromatography (silica gel/chloroform) gave a brown solid which remains unidentified, m.p. > 200 °C (lit.,[139] 121 °C).

Note:

• thionyl chloride and phosphorus pentachloride were also used as chlorinating agents instead of phosphoryl chloride in the above procedure without success.

Attempted preparation of 3-chloro-5-phenyl-1,2,4-triazine **234**

A solution of 5-phenyl-1,2,4-triazin-3-one (0.87 g, 5.03 mmol) and phosphoryl chloride (5 ml) was heated under reflux for 3 h at 120 °C. The brown solution was evaporated and poured on to ice (30 g). The brown solid was filtered and washed with 2M ammonia (5 ml) then water (5 ml) and dried (over anhydrous calcium chloride). The black tar was extracted with petroleum (b.p. 40–60 °C) and the solvent evaporated to afford a brown solid which is unidentified, m.p. > 200 °C.

Preparation of 3-chloro-5-phenyl-1,2,4-triazine **234**

A solution containing 5-phenyl-1,2,4-triazin-3-one (0.40 g, 2.31 mmol), "aged" (i.e. unpurified) phosphoryl chloride (2.20 g, 14.47 mmol) and triethylamine (0.48 g,

4.75 mmol) was heated under reflux for 40 min at 140 °C. The excess phosphoryl chloride was evaporated, the residue extracted with petroleum (5 x 20 ml), dried and the solvent evaporated to give a yellow solid which was reprecipitated from petroleum to afford 3-chloro-5-phenyl-1,2,4-triazine (0.33 g, 87%) as a yellow powder, m.p. 120–122 °C (lit.,[188] 121 °C); v_{max} 683, 756, 1153, 1244, 1539 and 1732 cm^{-1}; δ_H 7.55–7.70 (3 H, m, H-2,4,6), 8.19 (2 H, dd, J 8, 2, H-3,5) and 9.64 (1 H, s); δ_C 128.1 (2 CH), 129.6 (2 CH), 131.9 (4^{ry}, C-1), 133.6 (CH), 144.5 (CH, C-6'), 157.7 (4^{ry}, C-5') and 164.9 (4^{ry}, C-3'); m/z 191 (^{35}Cl-M$^+$, 33%), 163 (5), 128 (12) and 102 (100).

Preparation of 3-methoxy-5-phenyl-1,2,4-triazine 238

A solution of 3-chloro-5-phenyl-1,2,4-triazine (0.10 g, 0.52 mmol), sodium methoxide (600% excess) and methanol (10 ml) was stirred for 3 h at room temperature. The mixture was extracted with petroleum (3 x 10 ml) and the solvent evaporated. The white solid was reprecipitated from methanol to afford 3-methoxy-5-phenyl-1,2,4-triazine (0.07 g, 72%) as a white powder, m.p. 76–79 °C (lit.,[80] 77–78 °C); δ_H 4.26 (3 H, s, OCH$_3$), 7.56 (3 H, m, H-2,4,6), 8.19 (2 H, dd, J 8, 2, H-3,5), 9.41 (1 H, s); δ_C 55.8 (OCH$_3$), 127.8 (2 CH), 129.4 (2 CH), 132.8 (CH), 133.1 (4^{ry}, C-1), 141.5 (CH, C-6'), 157.9 (4^{ry}, C-5') and 165.8 (4^{ry}, C-3'); m/z 187 (M$^+$, 34%), 116 (16), 102 (100) and 89 (5).

Preparation of 1,2,4-triazin-5-one-3-thione-6-carboxylic acid 239

A solution of the disodium salt of mesoxalic acid (80.0 g, 0.4 mol) and thiosemicarbazide (45.5 g, 0.5 mol) in water (150 ml) was heated under reflux with stirring for 6 h. The reaction mixture was cooled, filtered and the filtrate was collected, acidified to pH1 with concentrated HCl, and left overnight at 4 °C. The solid was recrystallised from water to yield yellow/green crystals. Further recrystallisation from acetic acid afforded 1,2,4-triazin-5-one-3-thione-6-carboxylic acid (61.9 g, 90%) as yellow needles, m.p. 220–222 °C (lit.,[140] 244–246 °C); v_{max} 779, 1167, 1271, 1735

and 3468 cm^{-1}; δ_H (CD$_3$SOCD$_3$) 3.00–3.50 (1 H, bs, NH) and 13.69 (1 H, bs, COOH); δ_C (CD$_3$SOCD$_3$) 139.5 (4^{ry}, C-6), 150.6 (4^{ry}, C-5), 161.6 (4^{ry}, COOH) and 174.6 (4^{ry}, C-3).

Preparation of 3-(methylsulphanyl)-1,2,4-triazin-5-one-6-carboxylic acid 240

To a solution of 1,2,4-triazin-5-one-3-thione-6-carboxylic acid (17.3 g, 0.1 mol) in 1M sodium hydroxide (356 ml) was added iodomethane (6.9 ml, 0.1 mol) dropwise with stirring over 30 min. The mixture was then acidified to pH1 with concentrated HCl, concentrated to 125 ml *in vacuo* and left overnight at 4 °C. The solid was filtered, dried at 100 °C for 2 h, and recrystallised from acetic acid to afford 3-(methylsulphanyl)-1,2,4-triazin-5-one-6-carboxylic acid (15.9 g, 85%) as colourless needles, m.p. effervesced at 178 °C, resolidified, and then melted at 210–212 °C (lit.,[140] 212–214 °C).

Preparation of 1,2,4-triazine-3,5-dione-6-carboxylic acid 241

A solution of 3-(methylsulphanyl)-1,2,4-triazin-5-one-6-carboxylic acid (14.7 g, 78 mmol) in concentrated HCl (30 ml) and acetic acid (55 ml) was heated under reflux for 5 h. The reaction mixture was filtered, the insoluble material was washed with a little boiling acetic acid (20 ml) and the washings were added to the filtrate. The liquid was left at 4 °C overnight and the resulting solid was filtered and reprecipitated from acetic acid to afford 1,2,4-triazine-3,5-dione-6-carboxylic acid (6.0 g, 49%) as a white powder, m.p. 236–238 °C (lit.,[140] 237–238 °C).

Preparation of 1,2,4-triazine-3,5-dione (6-azauracil) 242

A solution of 1,2,4-triazine-3,5-dione-6-carboxylic acid (4.2 g, 27 mmol) in diphenyl ether (50 ml) was heated under reflux for 30 min at 190 °C. The mixture was cooled and the precipitate filtered and washed several times with ether (3 x 10 ml). The solid was sublimed *in vacuo* (200 °C /1mm Hg) to afford 6-azauracil (2.4 g, 77%) as a white powder, m.p. 276–278 °C (lit.,[140] 277–279 °C); δ_H (CD$_3$SOCD$_3$) 7.35

(1 H, s).

Preparation of 3,5-dichloro-1,2,4-triazine **232**

A mixture of 6-azauracil (1.0 g, 8.85 mmol), phosphoryl chloride (8.0 g, 52 mmol) and triethylamine (0.75 g, 7.43 mmol) was heated under reflux with stirring for 40 min. The excess solvent was evaporated and the brown oil was distilled (partially sublimed) at 1.5mm Hg/180 °C to give colourless needles. The crystals were extracted with petroleum (50 ml) and crystallised from the concentrated solution to afford 3,5-dichloro-1,2,4-triazine (60 mg, 6%) as colourless needles, m.p. 52–54 °C (lit.,[135] 55 °C).

Note:

* The product however decomposed rapidly and was thus stored under nitrogen at −20 °C.

Attempted preparation of 3,5-dichloro-1,2,4-triazine **232**

A mixture of 6-azauracil (1.0 g, 8.85 mmol) and phosphorus pentachloride (1.84 g, 8.85 mmol) was stirred at room temperature for 30 min and phosphoryl chloride (1 ml) was added dropwise and the mixture stirred for 10 min. The bright yellow solution was then heated under reflux for 10 min, cooled and the resulting brown oil was poured in to ice/water (300 g) and stirred for 2 h. The aqueous mixture was then extracted with petroleum (2 x 50 ml), dried and the solvent evaporated to give a small quantity of an orange oil which could not be distilled and was unidentified.

Preparation of 3,5-dichloro-1,2,4-triazine **232**

To 6-azauracil (1.0 g, 8.85 mmol) in phosphoryl chloride (10 ml) was added phosphorus pentachloride (3.68 g, 17.7 mmol) and triethylamine (2.68 g, 26.5 mmol) with stirring over 30 min. The mixture was then heated under reflux with stirring for 2 h and allowed to stand at room temperature for 24 h. The excess phosphoryl chloride was evaporated and the residue extracted with ether (5 x 20 ml), dried and the solvent

evaporated. The resulting yellow oil was distilled at 1.5mm Hg/160 °C to afford 3,5-dichloro-1,2,4-triazine (20 mg, 2%) as colourless needles, m.p. 50–54 °C (lit.,[135] 55 °C).

Preparation of 3,5-dichloro-1,2,4-triazine 232

To a solution containing triethylamine (0.66 g, 6.5 mmol) and ice-cold phosphoryl chloride (1.99 g, 13 mmol) was added 6-azauracil (0.37 g, 3.3 mmol) and the reaction mixture was heated under reflux with stirring for 15 min. After cooling the solution was extracted with hexane (3 x 50 ml) and the solvent evaporated to give a brown residue which was vacuum sublimed to afford 3,5-dichloro-1,2,4-triazine (80 mg, 8%) as colourless needles, m.p. 53–56 °C (lit.,[135] 55 °C).

Preparation of 3,5,6-trichloro-1,2,4-triazine 243

A solution containing 6-azauracil (2.5 g, 22.1 mmol), bromine (3,79 g, 24 mmol) and water (38 ml) was stirred at room temperature for 16 h and the colourless plates which formed were filtered and recrystallised from water to afford 5-bromo-6-azauracil (2.62 g, 64%) as colourless plates, m.p. 230–232 °C (lit.,[141] 232–234 °C). To 5-bromo-6-azauracil (1.60 g, 8.38 mmol) was immediately added phosphoryl chloride (3.85 g, 25.2 mmol), phosphorus pentachloride (3.5 g, 20 mmol) and triethylamine (2.5 g, 25 mmol). The mixture was heated with stirring under reflux for 2 h and then allowed to stand at room temperature for 24 h. The excess solvent was evaporated and the resulting residue extracted with anhydrous ether (5 x 100 ml), dried and the solvent evaporated. Distillation (55–60 °C, 0.05 mmHg) of the residue remaining from the ether phase gave 3,5,6-trichloro-1,2,4-triazine (1.18 g, 76%) as yellow plates, m.p. 62–63 °C (lit.,[141] 58–60 °C); v_{max} 763, 880, 1044, 1073, 1166, 1204, 1263, 1460 and 1487 cm^{-1}; δ_C 154.8 (4^{ry}, C-6), 157.0 (4^{ry}, C-5) and 160.9 (4^{ry}, C-3); m/z 185 (^{35}Cl-M$^+$, 30%), 157 (22), 122 (7) and 94 (100).

Preparation of 3,6-dichloro- 5-methoxy-1,2,4-triazine **244**

A solution of 3,5,6-trichloro-1,2,4-triazine (0.52 g, 2.81 mmol) and sodium methoxide (0.15 g, 2.81 mmol) was stirred at room temperature in methanol (20 ml) for 12 h, the solvent evaporated and the residue recrystallised from ethanol to afford 3,6-dichloro- 5-methoxy-1,2,4-triazine (0.38 g, 74%) as yellow plates, m.p. 61–62 °C (lit.,[142] 62–63 °C); δ_H 4.23 (3 H, s, OCH$_3$); δ_C 154.7 (4^{ry}, C-6), 156.0 (4^{ry}, C-5) and 161.7 (4^{ry}, C-3).

Preparation of 6-methyl-5-one-3-thione-1,2,4-triazine **247**

To a solution of thiosemicarbazide (45.5 g, 0.5 mol) in warm water (500 ml, 60 °C) was added pyruvic acid (40.5 g, 0.5 mol) with stirring. The reaction mixture was left overnight at 4 °C and the thiosemicarbazone was filtered. It was then dissolved in sodium hydroxide solution (1500 ml, 1M), was heated under reflux for 1 h, cooled, filtered and acidified with concentrated hydrochloric acid to pH1. The reaction mixture was then allowed to cool to room temperature and the product filtered and recrystallised from aqueous ethanol (50%) to afford 6-methyl-5-one-3-thione-1,2,4-triazine (57.2 g, 80%) as yellow plates, m.p. 210–213 °C (lit.,[143] 214–216 °C); δ_C (CD$_3$SOCD$_3$) 16.4 (CH$_3$), 148.7 (4^{ry}, C-6), 153.7 (4^{ry}, C-5) and 173.6 (4^{ry}, C-3); m/z 143 (M$^+$, 100%) and 85 (11).

Preparation of 6-methyl-3,5-dithione-1,2,4-triazine **249**

A reaction mixture containing 6-methyl-5-one-3-thione-1,2,4-triazine (10.0 g, 69.9 mmol), phosphorus pentasulphide (15.5 g, 69.9 mmol) and pyridine (300 ml) was heated under reflux for 1 h with stirring. The volume was reduced to 100 ml and the residue poured into ice/water (250 ml), allowed to cool and the orange powder filtered. The orange powder was dissolved in 0.02M sodium hydroxide (220 ml) and put on a Dowex 1 (formate) column (approximately 4cm x 16cm). After washing with water (50 ml) the column was eluted with 0.025M formic acid (3 litres). The eluate was neutralised by the addition of 2M sodium hydroxide and concentrated *in vacuo* to

100 ml. The concentrated solution was then adjusted to pH1 and shaken with ether (3 x 100 ml). The ether was dried (over anhydrous sodium sulphate), evaporated and reprecipitated from water to afford 6-methyl-3,5-dithione-1,2,4-triazine (7.62 g, 69%) as an orange powder, m.p. 214–216 °C (lit.,[143] 215–217 °C); δ_H (CD$_3$SOCD$_3$) 2.28 (CH$_3$); δ_C (CD$_3$SOCD$_3$) 19.8 (CH$_3$), 151.8 (4^{ry}, C-6), 169.6 (4^{ry}, C-5) and 180.6 (4^{ry}, C-3).

Attempted preparation of 6-methyl-3,5-bis(methylsulphanyl)-1,2,4-triazine 250

A solution of dimethyl sulphate (1.54 g, 16 mmol) was added with stirring to 6-methyl-3,5-dithione-1,2,4-triazine (2.0 g, 13 mmol) in aqueous potassium hydroxide (0.02 g in 50 ml water, 16 mmol). The reaction mixture was then heated under reflux with stirring for 8 h, cooled and aqueous ammonia (10%, 10 ml) added to destroy any excess dimethyl sulphate. The reaction mixture was extracted with ether (3 x 50 ml), washed with water (2 x 30 ml) and the organic layer dried and evaporated to give an orange powder which was shown to be starting material (by ^{13}C NMR).

Attempted preparation of 6-methyl-3,5-bis(methylsulphanyl)-1,2,4-triazine 250

A solution of iodomethane (2.44 g, 17.2 mmol) was added with stirring to 6-methyl-3,5-dithione-1,2,4-triazine (1.35 g, 8.49 mmol) in aqueous sodium hydroxide (0.05 g in 50 ml water). The reaction mixture was then placed at 4 °C for 4 h. The small amount of black product which precipitated was collected, washed with water (10 ml) and dried. Analysis revealed the product to be present however, only a very small amount of impure material was obtained.

Preparation of 6-methyl-3,5-bis(methylsulphanyl)-1,2,4-triazine 250

A solution of iodomethane (2.44 g, 17.2 mmol) was added with stirring to 6-methyl-3,5-dithione-1,2,4-triazine (1.35 g, 8.49 mmol) in aqueous sodium hydroxide (0.05 g in 50 ml water). The reaction mixture was then shaken vigorously at room temperature for 10 h. The solid was recrystallised from petroleum to afford 6-methyl-

3,5-bis(methylsulphanyl)-1,2,4-triazine as pale yellow plates in yields varying from 20–50%, m.p. 74–77 °C (lit.,[143] 75–76 °C); δ_C (CD$_3$SOCD$_3$) 12.0 (SCH$_3$), 13.3 (SCH$_3$), 18.3 (CH$_3$), 151.4 (4^{ry}, C-5), 164.7 (4^{ry}, C-6) and 169.4 (4^{ry}, C-3); m/z 187 (M$^+$, 63%), 112 (4) and 86 (100).

Preparation of 6-methyl-3-methylsulphanyl-5-methylsulphonyl-1,2,4-triazine **245**

To a solution of 6-methyl-3,5-bis(methylsulphanyl)-1,2,4-triazine (0.30 g, 1.60 mmol) in acetic acid (3 ml) was added dropwise with stirring at 5–8 °C a solution of potassium permanganate (0.42 g, 2.66 mmol) in water (15 ml). Thereafter the mixture was cooled to 0 °C and continued stirring for 1 h. Enough sodium metabisulphite was added to decolourise the solution and remove any manganese dioxide. The resulting mixture was extracted with dichloromethane (3 x 30 ml), dried, washed with water (20 ml) and then the solvent was evaporated. The product was recrystallised from dichloromethane to afford 6-methyl-3-methylsulphanyl-5-methylsulphonyl-1,2,4-triazine (0.20 g, 57%) as colourless prisms, m.p. 150–152 °C (lit.,[144] 157–158 °C; δ_H 2.72 (3 H, s), 2.84 (3 H, s) and 3.48 (3 H, s, SO$_2$CH$_3$); δ_C 12.7 (SCH$_3$), 19.2 (CH$_3$), 36.5 (SO$_2$CH$_3$), 158.4 (4^{ry}, C-5), 164.0 (4^{ry}, C-6) and 169.4 (4^{ry}, C-3); m/z 219 (M$^+$, 24%), 187 (73), 140 (10), 125 (5), 112 (27), 99 (12) and 86 (100).

Preparation of 5-methoxy-6-methyl-3-methylsulphanyl-1,2,4-triazine **252**

To a solution of 6-methyl-3-methylsulphanyl-5-methylsulphonyl-1,2,4-triazine (100 mg, 0.46 mmol) in anhydrous methanol (5 ml) was added sodium methoxide (24.8 mg, 0.46 mmol, freshly prepared) and the reactants were stirred together at room temperature for 6 h. The reaction mixture was then poured in to ice/water (10 ml) and the solution was extracted with ether (3 x 20 ml) and reprecipitated from toluene to afford 5-methoxy-6-methyl-3-methylsulphanyl-1,2,4-triazine (67.6 mg, 86%) as a pale yellow powder, m.p. 80–82 °C (lit.,[145] 79–80 °C); δ_H (CD$_3$SOCD$_3$) 2.72 (3 H, s), 2.84 (3 H, s) and 4.12 (3 H, s, OCH$_3$); δ_C (CD$_3$SOCD$_3$) 12.0 (SCH$_3$), 18.3 (CH$_3$), 55.4 (OCH$_3$), 151.9 (4^{ry}, C-5), 164.6 (4^{ry}, C-6) and 169.3 (4^{ry}, C-3).

Preparation of 5,6-diphenyl-1,2,4-triazin-3-one **254**

A solution of benzil (10.50 g, 50 mmol) in acetic acid (100 ml) was added to semicarbazide hydrochloride (7.00 g, 60 mmol) in water (20 ml). The reaction mixture was heated under reflux for 4 h, cooled to room temperature and poured in to ice/water (500 ml). The white powder was filtered and reprecipitated from acetic acid to afford 5,6-diphenyl-1,2,4-triazin-3-one (10.96 g, 88%) as a white powder, m.p. 223–224 °C (lit.,[147] 224–226 °C); δ_H (CD$_3$SOCD$_3$) 7.20–7.52 (10 H, m); δ_C (CD$_3$SOCD$_3$) 128.4 (2 CH), 128.5 (2 CH), 128.9 (2 CH), 129.4 (2 CH), 130.0 (CH), 131.7 (CH), 134.0 (4^{ry}), 135.2 (4^{ry}), 143.7 (4^{ry}, C-6), 155.3 (4^{ry}, C-5) and 168.2 (4^{ry}, C-3).

Preparation of 3-chloro-5,6-diphenyl-1,2,4-triazine **253**

A mixture of 5,6-diphenyl-1,2,4-triazin-3-one (5.60 g, 22.5 mmol) and phosphoryl chloride (11 ml) was heated in an oil bath at 150 °C for 50 min until evolution of gaseous hydrochloric acid ceased. The cooled mass was added with stirring to ice (200 ml) and the yellow solid collected and washed with water (30 ml). It was then thrice triturated with sodium hydroxide (30 ml, 2% aq.) at 50 °C, filtered, washed with water (20 ml) and reprecipitated from toluene to afford 3-chloro-5,6-diphenyl-1,2,4-triazine (4.81 g, 80%) as an orange powder, m.p. 154–156 °C (lit.,[146] 156–157 °C); δ_H 7.26-7.61 (10 H, m); δ_C 128.7 (2 CH), 128.8 (2 CH), 129.5 (2 CH), 130.0 (2 CH), 130.1 (CH), 131.6 (CH), 134.3 (4^{ry}), 134.5 (4^{ry}), 154.2 (4^{ry}, C-6), 158.0 (4^{ry}, C-5) and 162.3 (4^{ry}, C-3).

Mono-triazine displacement reactions

Preparation of bisphenol A mono-(5,6-diphenyl-1,2,4-triazin-3-yl)ether **256**

To a stirred solution of sodium hydride (60%, 59.4 mg, 1.49 mmol, 1.1 eq) and anhydrous tetrahydrofuran (20 ml) was added bisphenol A (307.8 mg, 1.35 mmol) in tetrahydrofuran (20 ml) dropwise and the mixture was warmed to 40 °C. The 3-chloro-5,6-diphenyl-1,2,4-triazine (363.2 mg, 1.36 mmol) in tetrahydrofuran (30 ml) was then added dropwise to the reaction mixture and stirring was continued under nitrogen for

12 h. The solvent was evaporated and the residue extracted with dichloromethane (2 x 50 ml), washed with brine (20 ml) then water (50 ml), dried and the solvent evaporated to give a pale yellow solid which was purified by column chromatography [silica gel, ether:petrol (1:1)] rf 0.4 and recrystallised from anhydrous toluene to give bisphenol A mono-(5,6-diphenyl-1,2,4-triazin-3-yl)ether (0.26 g, 42%) as yellow needles, m.p. 60–64 °C (Found: M+, 459.4476. $C_{30}H_{25}N_3O_2$ requires M, 459.4464); v_{max} 780, 1240, 1542, 1600 and 3600 cm-1 (OH); δ_H 1.72 (6 H, s, 2 CH_3), 7.22–7.57 (10 H, m) and 6.72–7.18 (8 H, AB pattern); δ_C 31.8 (2 CH_3), 115.4 (4ry), 127.6 (2 CH), 128.3 (2 CH), 128.5 (2 CH), 128.6 (2 CH), 128.8 (2 CH), 128.9 (2 CH), 129.3 (2 CH), 129.6 (2 CH), 130.0 (CH), 131.3 (CH), 131.7 (4ry), 132.3 (4ry), 135.3 (4ry), 135.5 (4ry), 148.4 (4ry), 154.3 (4ry, C-6), 154.5 (4ry), 159.5 (4ry, C-5) and 166.5 (4ry, C-3); m/z 459 (M+, 15%), 442 (51), 345 (6), 233 (18), 192 (12), 178 (100), 165 (16) and 104 (9).

Preparation of 2,2'-isopropylidenebis-p-[phenoxy(3,6-dichloro-1,2,4-triazine)] 257

To a stirred solution of sodium hydride (60%, 118.8 mg, 2.97 mmol, 1.1eq) and anhydrous tetrahydrofuran (20 ml) was added bisphenol A (307.8 mg, 1.35 mmol) in anhydrous tetrahydrofuran (20 ml) dropwise and the mixture was warmed to 40 °C. The 3,5,6-trichloro-1,2,4-triazine (500 mg, 2.70 mmol) in anhydrous tetrahydrofuran (30 ml) was then added dropwise to the reaction mixture and stirring was continued under nitrogen for 24 h. The solvent was evaporated and the residue extracted with dichloromethane (2 x 80 ml), washed with brine (50 ml) then water (50 ml), dried and the solvent evaporated to give a pale yellow solid which was purified by column chromatography [silica gel, ether:petrol (2:1)] and recrystallised from anhydrous toluene to afford 2,2'-isopropylidenebis-p-[phenoxy(3,6-dichloro-1,2,4-triazine)] (70.7 mg, 10%) as yellow needles, m.p. 178–181 °C (Found: C, 48.3; H, 2.7; N, 16.25. $C_{21}H_{14}N_6O_2Cl_4$ requires C, 48.1; H, 2.7; N, 16.0%)(Found: M+, 524.1917. $C_{21}H_{14}N_6O_2Cl_4$ requires M, 524.1914); v_{max} 780, 1240, 1545 and 1600 cm-1; δ_H 2.62 (6 H, s, 2 CH_3) and 7.04–7.38 (8 H, m); δ_C 31.8 (2 CH_3), 120.7 (4ry), 121.1

(4 CH), 128.1 (4 CH), 129.1 (2 4^{ry}), 148.5 (2 4^{ry}), 154.4 (2 4^{ry}, C-6), 160.7 (2 4^{ry}, C-3) and 164.0 (2 4^{ry}, C-5); *m/z* 524 (M$^+$, 15%), 509 (100), 366 (90), 236 (18), 213 (65), 167 (30), 149 (35) and 125 (52).

Attempted preparation of 2,2'-isopropylidenebis-*p*-[phenoxy(6-methyl-3-methylsulphanyl-1,2,4-triazine)] **258**

To a stirred solution of sodium hydride (60%, 118.8 mg, 2.97 mmol, 1.1 eq.) and anhydrous tetrahydrofuran (35 ml) was added bisphenol A (307.8 mg, 1.35 mmol) in anhydrous tetrahydrofuran (20 ml) dropwise. The 6-methyl-3-methylsulphanyl-5-methylsulphonyl-1,2,4-triazine (591 mg, 2.70 mmol) in anhydrous tetrahydrofuran (15 ml) was then added dropwise to the reaction mixture and stirring was continued under nitrogen for 4 h. The solvent was evaporated and the residue extracted with dichloromethane (2 x 50 ml), washed with brine (30 ml) then water (30 ml), dried and the solvent evaporated to give a pale yellow powder which was shown by NMR and tlc to be a mixture of bisphenol A and possible decomposition products of the triazine. Note:

- Attempts at lower temperature i.e. 0 °C resulted in full recovery of starting materials.

MOPAC 5.0 calculations

All calculations were carried out using the computer program MOPAC 5.0 using the Hamiltonian AM1 on a Sun workstation. 'Dummy atoms' were used to define the axes and the calculations were carried out using double precision accuracy. The input file was in the form of cartesian coordinates. The geometry optimised output was fed into a molecular modelling program to validate the calculation. The LUMO (lowest unoccupied molecular orbital) and HOMO (highest occupied molecular orbital) energy coefficients were displayed in the output file (in electron volts) and the values obtained for HOMO and LUMO are shown for the compounds studied in Chapter 2 (pages 58–60).

C. Bis dienophile synthesis

1. Preparation of bis-alkynes

A. Synthesis of 3-chloropropenals

Distilled phosphoryl chloride (7.4 ml, 83 mmol) was added dropwise over 30 min to N,N-dimethylformamide (40 ml) under an atmosphere of nitrogen. Stirring was continued for 30 min and a red solution was obtained. The corresponding diketone was then added (21 mmol) in one portion. The reaction was heated to 60 °C under nitrogen with stirring for 5 h. After cooling to room temperature the mixture was added to ice/water (100 ml) and the dark aqueous solution neutralised by the portionwise addition of solid sodium bicarbonate. Once at pH7 the mixture was left overnight at 4 °C and the resultant orange bis-(3-chloropropenal) was filtered off, washed with water (20 ml) and dissolved in dichloromethane (150 ml). This solution was washed with dilute brine (100 ml) then dried, and the solvent evaporated to give the dialdehyde. Attempts at reprecipitation of the bis-3-chloropropenals proved fairly unsuccessful and they were therefore judged to be of sufficient purity (by NMR) to be used without purification.

Preparation of 2,2'-dichloro-3,3'-(oxy-p-phenylene)bis(-E-prop-2-enal) **275**

The method of C1A was followed using bis-(4-acetylphenyl)ether (5.33 g, 21 mmol) to give 2,2'-dichloro-3,3'-(oxy-p-phenylene)bis(-E-prop-2-enal) (3.61 g, 50%) as an orange solid, m.p. 99–102 °C (lit.,[156] 100–104 °C); δ_H 6.63 (2 H, d, J 7), 7.08 and 7.76 (8 H, AB pattern, Ar-H) and 10.20 (2 H, d, J 7); δ_C 119.9 (4 CH), 123.9, (2 CH), 129.3 (4 CH), 131.2 (2 4ry), 151.0 (2 4ry), 159.8 (2 4ry) and 191.5 (2 4ry, C=O).

Preparation of 2,2'-dichloro-3,3'-(thio-p-phenylene)bis(-E-prop-2-enal) **276**

The method of C1A was followed using bis-(4-acetylphenyl)sulphide (5.67 g, 21 mmol) to give 2,2'-dichloro-3,3'-(thio-p-phenylene)bis(-E-prop-2-enal) (5.21 g, 69%) as an orange solid, m.p. 105–107 °C (lit.,[156] 106–110 °C); δ_H 6.67 (2 H, d,

J 7), 7.39 and 7.70 (8 H, AB pattern, Ar-H) and 10.21 (2 H, d, J 7); δ_C 124.7 (2 CH), 128.4 (4 CH), 131.1 (4 CH), 134.3 (2 4ry), 140.0 (2 4ry), 151.4 (2 4ry) and 191.4 (2 4ry, C=O).

B. Preparation of bis-alkynes

A solution of sodium hydroxide (1.92 g, 48 mmol) in dioxan/water (3:2, 73 ml) was heated to 80 °C and the bis-(3-chloropropenal)(12 mmol) was added in one portion. The reaction mixture darkened on addition and stirring was continued for a further 30 min. The reaction mixture was subsequently cooled to room temperature, poured in to brine (50 ml) and extracted with dichloromethane (2 x 50 ml), dried and the solvent evaporated to give a dark syrup which was purified by dry flash column chromatography.

Dry flash chromatography

In this procedure the sinter was filled with silica (silica gel (Merck 'Kieselgel' 60H tlc grade)) and compacted by applying suction and pressing it down. The column was then covered with the least polar component of the eluant mixture and sucked dry. The mixture to be separated was then pre-adsorbed on to a small amount of the silica gel and applied to the top of the silica gel. The separation is achieved by elution with equal volumes of solvent mixtures of increasing polarity and the column is sucked to dryness between successive applications of solvent.

Preparation of 4,4'-diethynyldiphenyl ether 220

The method of C1B was followed using 2,2'-dichloro-3,3'-(oxy-p-phenylene)bis(-E-prop-2-enal) (4.15 g, 12 mmol) to afford 4,4'-diethynyldiphenyl ether (1.07 g, 41%) as a white powder, m.p. 76–77 °C (lit.,[130] 77–77.5 °C); ν_{max} 2102 (alkyne) and 3285 (CH) cm^{-1}; δ_C (CD$_3$SOCD$_3$) 80.5 (2 CH), 83.1 (2 4ry), 117.3 (2 4ry, C-4), 119.2 (4 CH, C-2,6), 134.0 (4 CH, C-3,5) and 156.6 (2 4ry, C-1).

Preparation of 4,4'-diethynyldiphenyl sulphide **274**

The method of C1B was followed using 2,2'-dichloro-3,3'-(thio-*p*-phenylene)bis(-*E*-prop-2-enal) (4.34 g, 12 mmol) to afford 4,4'-diethynyldiphenyl sulphide (1.4$\bar{0}$ g, 50%) as a pale yellow powder, m.p. 115–118 °C (lit.,[189] 117–120 °C); ν_{max} 2102 (alkyne) and 3265 (CH) cm^{-1}; δ_C (CD$_3$SOCD$_3$) 82.2 (2 CH), 83.1 (2 4^{ry}), 121.1 (2 4^{ry}, C-4), 131.0 (4 CH, C-2,6), 133.0 (4 CH, C-3,5) and 135.6 (2 4^{ry}, C-1).

2. Mono enamine synthesis

Preparation of 1-(1-cyclohexenyl)pyrrolidine **284**

A solution containing cyclohexanone (9.9 g, 0.10 mol) and pyrrolidine (12.0 g, 0.17 mol) in toluene (150 ml) was heated under reflux with removal of water using Dean and Stark apparatus for 4 h. The solvent was evaporated and the residue distilled to afford 1-(1-cyclohexenyl)pyrrolidine (13.7 g, 91%) as a colourless oil, (b.p. 110–112 °C at 12 mmHg)(lit.,[163] 109–111 at 12 mmHg); δ_H 1.50–1.68 (4 H, m), 1.75–1.80 (4 H, m), 2.02–2.18 (4 H, m), 2.91–3.02 (4 H, m) and 4.20–4.25 (1 H, m); δ_C 23.1 (CH$_2$), 23.4 (CH$_2$), 24.6 (2 CH$_2$), 25.2 (CH$_2$), 27.6 (CH$_2$), 47.4 (2 CH$_2$), 93.6 (CH) and 143.3 (4^{ry}).

3. Synthesis of bis-enamines

Attempted preparation of oxy-*p*-phenylenebis-(2-pyrrolidinoethene) **288**

A solution containing bis-(4-acetylphenyl)ether (6.0 g, 23.6 mmol), pyrrolidine (5.7 g, 80.2 mmol) and *p*-toluenesulphonic acid (200 mg) was heated under reflux in toluene for 4h, with removal of water using a Dean and Stark apparatus. The toluene was evaporated and the residue separated by column chromatography (ether) to afford 2 fractions one of which (rf 0.6) was starting material and the other base line material was a black film, m.p. >300 °C. The reaction was repeated without *p*-toluenesulphonic acid, however similar results occurred.

Preparation of α-ketocyclohexylidenetriphenylphosphorane **291**

The salt (1-ethoxycarbonylpentyl)triphenylphosphonium bromide* (4.8 g, 9.98 mmol) was dissolved in t-butanol (50 ml) and potassium t-butoxide (1.23 g, 109.8 mmol) was added with stirring under nitrogen. The reaction mixture was heated under reflux with stirring for 12 h under nitrogen, the solvent evaporated and the reaction mixture partitioned between dichloromethane (200 ml) and water (100 ml). The dichloromethane extract was separated, dried, the solvent evaporated and the oil triturated in ether (10 ml) to afford α-ketocyclohexylidenetriphenylphosphorane (2.1 g, 60%) as a pale yellow powder, m.p. 241–242 °C (lit.,[164] 243–245 °C); δ_H 1.72–1.83 (6 H, m, 3 CH$_2$), 2.21–2.32 (2 H, m, CH$_2$) and 7.18–7.26 (15 H, m); δ_C 24.7 (CH$_2$), 26.1 (CH$_2$), 27.5 (CH$_2$), 37.1 (CH$_2$), 59.1 (4^{ry}), 126.6 (3 4^{ry}), 128.9 (6 CH), 132.8 (3 CH), 133.9 (6 CH) and 188.7 (4^{ry}, C=O); δ_P 17.30.

* donated by Dr. Alan Aitken

Attempted preparation of 2,2'-terephthaldiylidenedicyclohexanone **293**

The ylid α-ketocyclohexylidenetriphenylphosphorane (1.0 g, 2.86 mmol) was heated under reflux in anhydrous toluene (20 ml) with terephthalaldehyde (0.19 g, 1.42 mmol) for 24 h under nitrogen, the solvent was evaporated and the residue taken up in dichloromethane (50 ml), washed with water (20 ml), dried and the solvent evaporated to give a yellow oil. This oil was triturated in ether (15 ml) to remove most of the triphenylphosphine oxide (0.41 g, 1.47 mmol) and the residue purified by column chromatography (silica gel, ether) to give 3 fractions.

Firstly, a yellow powder (29.2 mg, 7%) was shown to be 2,2'-terephthaldiylidenedicyclohexanone **293**, m.p. 180–185 °C (dec.); v_{max} 1650–1665 (C=C) and 1680 cm^{-1} (C=O) ; δ_H 1.71–1.82 (4 H, m), 1.84–1.98 (4 H, m), 2.48–2.51 (4 H, m), 2.81–3.00 (4 H, m), 7.42–7.52 (4H, s) and 7.78–7.80 (2 H, s).

Secondly, a yellow oil (100 mg, 0.47 mmol) was shown to be 2-(*p*-formylbenzylidene)cyclohexanone **294.** However, this oil did not solidify after trituration or cooling and hence was not of sufficient purity for CHN analysis or melting

point; v_{max} 1650–1665(C=C), 1680 (C=O), 1700 (C=O); δ_H 1.70–1.74 (2 H, m), 1.81–1.86 (2 H, m), 2.41–2.45 (2 H, m), 2.83–2.85 (2 H, m), 7.30–7.58 (4 H, m), 7.81–7.87 (1H, s) and 10.18 (1 H, s).

Finally, triphenylphosphine oxide (40mg, 0.14 mmol) was obtained as colourless needles, m.p. 152–153 °C (lit.,[190] 156–158 °C); δ_H 7.42–7.71 (15 H, m); δ_P 28.58.

Note:

• Variations in reaction time (48 h) and solvent (N,N-dimethylformamide) gave very little improvement in the quantity of 2,2'-terephthaldiylidenedicyclohexanone obtained.

Preparation of 2,2'-(α,α'-dihydroxy-1,4-xylylene)dicyclohexanone 295

A solution of diisopropylamine (distilled from potassium hydroxide, 2.65 g, 26.2 mmol) in anhydrous tetrahydrofuran (20 ml) was cooled to –30 °C under nitrogen and butyllithium in hexane (after estimation of molarity by titration, 9.5 ml, 23.8 mmol) was added. After stirring for 10 min, cyclohexanone (distilled, 2.34 g, 23.8 mmol) in anhydrous tetrahydrofuran (30 ml) was added dropwise to the solution and the reaction mixture was stirred for 30 min at –78 °C. Terephthalaldehyde (2.00 g, 14.9 mmol) in anhydrous tetrahydrofuran (8 ml) was added and the reaction mixture was stirred for 1 h, quenched with saturated ammonium chloride (50 ml) and stirred at room temperature for 1 h. The reaction mixture was extracted with ether (3 x 30 ml), washed with water (60 ml), dried and the solvent evaporated. Column chromatography (silica gel, ether) followed by recrystallisation from ethanol afforded 2,2'-(α,α'-dihydroxy-1,4-xylylene)dicyclohexanone (2.42 g, 52%) as colourless needles, m.p. 159–161 °C (Found: C, 72.3; H, 8.2; $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.9%); v_{max} 1300 (OH), 1680 (C=O) and 3450 cm^{-1} (OH); δ_H 1.65–1.82 (4 H, m), 2.01–2.14 (4 H, m), 2.27–2.47 (4 H, m), 2.51–2.68 (4 H, m), 4.02 (2 H, bs, OH), 4.71–4.78 (2 CH, m), 5.32–5.40 (2 CH, d, J 6) and 7.26–7.32 (4 CH, s); δ_C 24.7 (2 CH$_2$), 24.8 (2 CH$_2$), 30.8 (2 CH$_2$), 42.7 (2 CH$_2$), 70.5 (2 CH), 74.5 (2 CH), 125.6 (2 CH), 127.1 (2 CH),

140.2 (2 4^{ry}) and 214.5 (2 4^{ry}, C=O); m/z 312 (M$^+$, 12%), 232 (27), 214 (50), 185 (33), 157 (7), 135 (43), 115 (16), 105 (31) and 98 (100).

Preparation of 2,2'-terephthaldiylidenedicyclohexanone 293

A solution of 2,2'-(α,α'-dihydroxy-1,4-xylylene)dicyclohexanone (2.00 g, 6.412 mmol) in anhydrous toluene (15 ml) was stirred at 0 °C with stirring with a catalytic amount of p-toluenesulphonic acid (2 mg) for 1 h. The reaction mixture was washed with a saturated sodium bicarbonate solution (30 ml), dried and the solvent evaporated to give a yellow solid which was reprecipitated from toluene to afford 2,2'-terephthaldiylidenedicyclohexanone (1.17 g, 62%) as a yellow powder, m.p. 180–185 °C (dec.)(Found: M$^+$, 294.1621. C$_{20}$H$_{22}$O$_2$ requires M, 294.1620); v_{max} 1650–1665(C=C) and 1680 cm^{-1} (C=O); δ_H 1.71–1.82 (4 H, m), 1.84–1.98 (4 H, m), 2.48–2.51 (4 H, m), 2.81–3.00 (4 H, m), 7.42–7.52 (4H, s) and 7.78–7.80 (2 H, s); δ_C 23.8 (2 CH$_2$), 24.3 (2 CH$_2$), 29.6 (2 CH$_2$), 40.8 (2 CH$_2$), 130.79 (4 CH, Ar), 137.2 (2 4^{ry}), 137.7 (2 4^{ry}), 137.8 (2 CH) and 202.0 (2 C=O); m/z 294 (M$^+$, 66%), 265 (38), 237 (39), 211 (19), 185 (54), 149 (100), 129 (42) and 97 (56).

Note:

- Reaction attempts at room temperature resulted in formation of a black solid which is unidentified and a decreased yield of the product.

In situ bis-enamine formation: 3,3'-terephthalylidenebis(2-pyrrolidinocyclohexene) 289

A solution containing 2,2'-terephthaldiylidenedicyclohexanone (0.50 g, 1.70 mmol) and pyrrolidine (0.24 g, 3.4 mmol) was heated under reflux under nitrogen in toluene (20 ml) for 3 h. An aliquot of the reaction mixture was analysed by ^{1}H NMR and the characteristic alkene proton at δ 4.85 was observed and the IR spectrum showed the characteristic alkenyl C-H stretch at 3020 cm^{-1}. All attempts at isolation of the bis-enamine by evaporation of the pyrrolidine and extraction with dichloromethane proved unsuccessful and resulted in the apparent decomposition of the enamine.

4. Preparation of *o*-ethynyl phenols

Attempted preparation of 2,2'-dibromobisphenol A **306**

A solution of bisphenol A (11.4 g, 0.05 mol) in dichloromethane (60 ml) and ether (70 ml) was stirred at 0 °C. A solution of bromine (16.0 g, 0.10 mol) in dichloromethane (30 ml) was then added at 0 °C and the reaction mixture was stirred at room temperature for 6 h. The solvent was evaporated to give a purple gelatinous solid which was shown to be a mixture of 2-mono and 2,2'-dibromo products by NMR.

Preparation of 2,2'-dibromobisphenol A **306**

A solution of bisphenol A (11.4 g, 0.05 mol) in dichloromethane (60 ml) and ether (70 ml) was stirred under nitrogen. A solution of bromine (16.0 g, 0.10 mol) in dichloromethane (30 ml) was then added slowly with mechanical stirring and the reaction mixture was heated under reflux with stirring under nitrogen for 4 h. The solution was washed with water (3 x 100 ml) until the aqueous layer was neutral and the solvent was dried and evaporated to give a red solid. Recrystallisation from ether/petrol (1:1, with charcoal) afforded 2,2'-dibromobisphenol A (15.0 g, 78%) as colourless cubes, m.p. 93–95 °C (lit.,[172] 95.9 °C); δ_H 1.55 (6 H, s, 2 CH$_3$), 5.52 (2 H, s, OH), 6.92 (2 H, d, J 8, H-6), 7.04 (2 H, dd, J 8, 2, H-5) and 7.31 (2 H, d, J 2, H-3); m/z (CI) 384 (M$^+$, 100%), 275 (16) and 197 (23).

Preparation of copper (I) iodide **314**[173]

A solution containing potassium iodide (36.5 g, 0.22 mol) and sodium thiosulphatepentahydrate (28.0 g, 0.11 mol) was made up in a 100 ml volumetric flask. A solution containing copper sulphatepentahydrate (25.0 g, 0.1 mol) in water (150 ml) was then added to the first solution from a burette with continuous rapid stirring until no further precipitation occurred. The dense white precipitate was allowed to settle and filtered, washed with water (50 ml), ethanol (20 ml) and ether (20 ml). The product was powdered, air-dried and was purified by Soxhlet extraction in tetrahydrofuran for 6 h before being dried in vacuo over sulphuric acid and stored in the dark.

Attempted preparation of bis-*o*-(phenylethynyl)phenol A **305**

A solution containing 2,2'-dibromobisphenol A (400 mg, 1.04 mmol), anhydrous triethylamine (10 ml) and dichlorobis(triphenylphosphine)palladium (120 mg, 0.17 mmol) was stirred together at room temperature under nitrogen for 10 min. Solid copper(I) iodide (32 mg, 0.17 mmol) was then added to the reaction mixture. Phenylacetylene (dried and distilled from potassium hydroxide, 230 mg, 2.29 mmol) was added to the reaction mixture which was then heated under reflux with stirring for 10 h. The triethylamine was then evaporated, water (20 ml) was added to the residue and the mixture was extracted with dichloromethane (2 x 100 ml), dried and the solvent evaporated. Column chromatography [silica gel, ether:petrol (1:1)] gave 2 fractions.

Firstly, (rf 0.9) a yellow powder was shown to be 1,4-diphenylbutadiyne (150 mg, 0.84 mmol), m.p. 85–87 °C (lit.,[175] 86–87 °C); v_{max} 900, 1150, 1200, 1400, 1499, 1680, 2150, 2200 and 3080 cm^{-1}; δ_C 73.9 (2 4^{ry}), 81.5 (2 4^{ry}), 121.7 (2 4^{ry}), 128.4 (4 CH), 129.1 (2 CH) and 132.4 (4 CH).

Secondly, (rf 0.7) colourless cubes were shown to be 2,2'-dibromobisphenol A (354 mg, 89% recovery) as colourless cubes, m.p. 93–95 °C (lit.,[172] 95.9 °C); δ_H 1.55 (6 H, s, 2 CH$_3$), 5.52 (2 H, s, OH), 6.92 (2 H, d, *J* 8, H-6), 7.04 (2 H, dd, *J* 8, 2, H-5) and 7.31 (2 H, d, *J* 2, H-3).

Note:

- Variations in reaction time (24–48 h), solvent type (*N,N*-dimethylformamide) and reaction concentrations (i.e. amount of palladium catalyst or copper iodide) did not result in any bis-*o*-ethynylphenol being observed.

Attempted preparation of 2,2'-diiodobisphenol A **321**[176]

A solution of 2,2'-dibromobisphenol A (2.00 g, 5.21 mmol) and iodine (0.78 g, 3.07 mmol) was heated to 50 °C and fuming nitric acid (1 ml) was added dropwise with stirring during 30 min. The reaction mixture was then heated under reflux for 15 min with stirring, the solution was cooled, poured into ice/water (100 ml) and

stirred for 1 h. The reaction mixture was then extracted with dichloromethane (3 x 50 ml), dried and the solvent evaporated to give a red solid which remains unidentified.

Attempted preparation of 2,2'-diiodobisphenol A **321**[177]

A solution containing 2-iodophenol (5.00 g, 0.02 mol), acetone (0.30 g, 5.23 mmol) and concentrated hydrochloric acid (0.21 g, 5.90 mmol) was stirred for 3 days at 40 °C. Acetic acid (40%, 5 ml) was then added to the reaction mixture and stirring was continued for 1 h. The reaction mixture was extracted with dichloromethane (3 x 25 ml), dried and evaporated to give a black solid which was shown to be mainly starting material and a base line material which was not the required product but was not identified.

Preparation of 4,4'-diacetoxybiphenyl **324**

Bisphenol (11.16 g, 0.06 mol) and acetic anhydride (200 ml) was heated under reflux for 4 h, the reaction cooled and the solid filtered, washed with ether (30 ml) and dried. Recrystallisation from acetic acid/water afforded 4,4'-diacetoxybiphenyl (13.77 g, 85%) as colourless plates, m.p. 190–192 °C (lit.,[179] 190–191 °C); δ_H 2.31 (6 H, s, 2 CH$_3$), 7.17 and 7.53 (8 H, AA'BB', Ar-H); δ_C 21.7 (2 CH$_3$), 121.4 (4 CH), 128.3 (4 CH), 148.4 (2 4^{ry}), 149.0 (2 4^{ry}) and 170.1 (2 4^{ry}, C=O).

Preparation of 4,4'-dihydroxy-3,3'-biacetophenone **325**

A solution of 4,4'-diacetoxybiphenyl (5.00 g, 0.02 mol) in nitrobenzene (50 ml) was stirred and aluminium chloride (5.19 g, 0.04 mmol, 2.1 eq.) was added portionwise to the reaction mixture. The reaction was heated under reflux for 48 h, cooled, added to ice (200 g) and concentrated hydrochloric acid (10 ml) was added and stirring was continued for 2 h. The reaction mixture was extracted with dichloromethane (3 x 50 ml), washed with water (25 ml) and the solvent dried and evaporated. The solid was recrystallised from ethanol to afford 4,4'-dihydroxy-3,3'-biacetophenone (1.51 g, 28%) as colourless needles, m.p. 218–220 °C (lit.,[180] 219–220 °C); δ_H 2.68 (6 H, s,

2 CH$_3$), 7.08 (2 H, dd, J 8, 2 H-5,5'), 7.65 (2 H, d, J 2, H-6,6') and 7.80 (2 H, d, J 8, H-3,3'), OH not apparent.
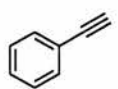
Notes:

- Lower reaction temperatures (for example room temperature in dichloromethane) and variation of reaction times (24–36 h) did not result in the required compound being synthesised, starting material was recovered.

- The addition of 4,4'-diacetoxybiphenyl to a mixture of aluminium chloride and nitrobenzene resulted in the formation of biphenol only.

- Larger scale reaction attempts also proved unsuccessful and gave starting material only.

Preparation of 2,2'-diethynyl-4,4'-biphenol **322**

A mixture of 4,4'-dihydroxy-3,3'-biacetophenone (0.80 g, 2.96 mmol) and phosphorus pentachloride (1.44 g, 6.92 mmol) were heated in toluene (5 ml) for 1 h to 80 °C. The reaction mixture was cooled to room temperature and anhydrous ether (20 ml) was added. It was then added dropwise with stirring to a suspension of sodamide in liquid ammonia [prepared from sodium (2.0 g) in liquid ammonia (80 ml)] and the reaction was continued stirring for 2 h and solid ammonium chloride (3.0 g) was then added. Extraction with ether (3 x 50 ml) gave 2,2'-diethynyl-4,4'-biphenol (34.6 mg, 5%) as colourless needles, m.p. 128–130 °C (lit.,[170] 129–130 °C).

Note:

- Several attempts varying reaction times made no appreciable difference to yield.

Preparation of 4,4'-isopropylidenebis(phenyl) diacetate **330**

A solution of bisphenol A (9.12 g, 0.04 mol) and acetic anhydride (200 ml) was heated under reflux for 4 h, the reaction cooled and the solid filtered, washed with ether (50 ml) and dried. Recrystallisation from acetic acid/water afforded 4,4'-isopropylidenebis(phenyl) diacetate (10.23 g, 82%) as colourless needles, m.p. 64–65 °C (lit.,[182] 66–68 °C); δ_H 1.52 (6 H, s), 2.24 (6 H, s) and 6.92 and 7.21 (8 H,

AA'BB', Ar-H); δ_C 31.4 (2 CH$_3$), 42.9 (2 OAc), 121.4 (4 CH), 122.2 (4^{ry}), 128.3 (4 CH), 148.4 (2 4^{ry}), 149.0 (2 4^{ry}) and 170.1 (2 4^{ry}).

Preparation of bis-o-(acetyl)phenol A **328**

A solution of 4,4'-isopropylidenebis(phenyl) diacetate (5.00 g, 0.02 mol) in nitrobenzene (50 ml) was stirred and aluminium chloride (5.19 g, 0.04 mmol, 2.1 eq.) was added portionwise to the reaction mixture. The reaction was heated under reflux for 48 h, cooled, added to ice (50 g) and conc. hydrochloric acid (10 ml) was added and stirring was continued for 2 h. The reaction mixture was extracted with dichloromethane (3 x 50 ml), washed with water (30 ml) and the solvent dried and evaporated. The solid was reprecipitated from ethanol and shown to be a mixture containing starting material and product. Attempted separation of the mixture by recrystallisation from toluene was partly successful and gave bis-o-(acetyl)phenol A as an impure white powder (1.25 g, 20%), m.p. 105–107 °C (lit.,[183] 107–109 °C); δ_H 2.63 (6 H, s, 2 CH$_3$), 6.95 (2 H, dd, J 8, 2, H-6,6'), 7.42 (2 H, d, J 2, H-2,2') and 7.64 (2 H, d, J 8, H-5,5'), OH not apparent.
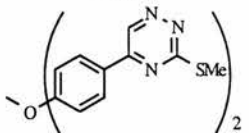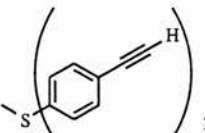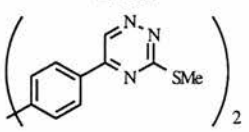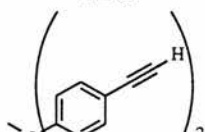
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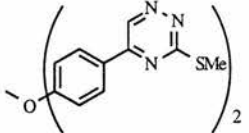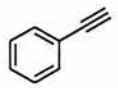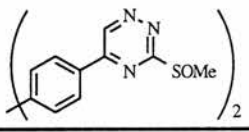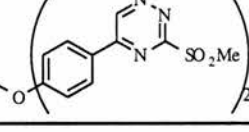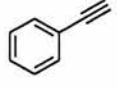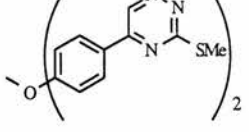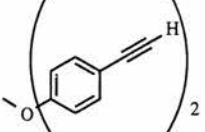
- Variations in reaction quantities, reaction times, solvent and reaction procedure always resulted in mixtures which were not easily separated and the reaction was abandoned.
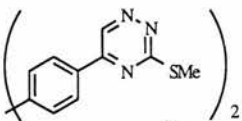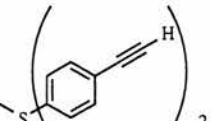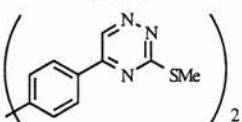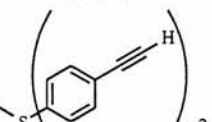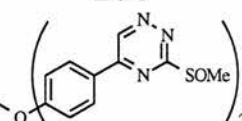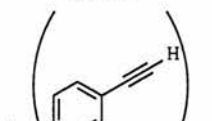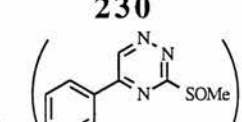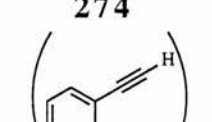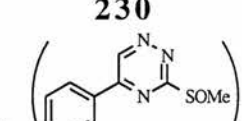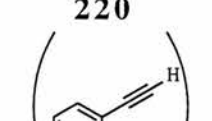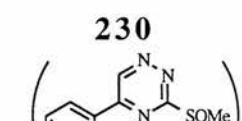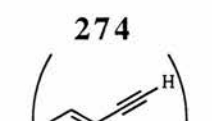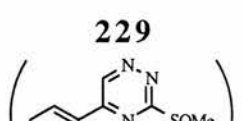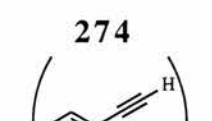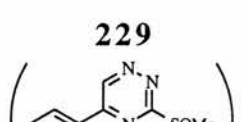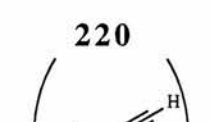
D. Diels-Alder reaction attempts
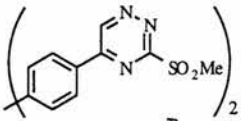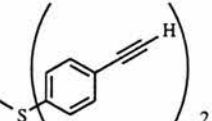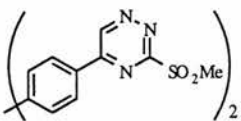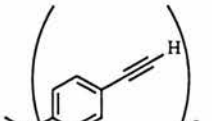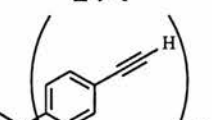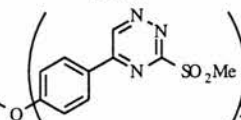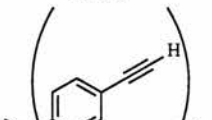
1. General procedure for Diels-Alder reactions with alkynes

A solution of the bis-1,2,4-triazine (1.19 mmol) and alkyne (1.19 mmol) was heated under reflux with stirring or stirred at room temperature in an anhydrous solvent for a certain time under nitrogen. The reaction was monitored by tlc (ether:petrol 40/60). The solvent was evaporated and the residue extracted with dichloromethane (3 x 25 ml), washed with water (10 ml), dried and the solvent evaporated. The residue was then

analysed by NMR and tlc. The following combinations were carried out. In the table the symbol * indicates that the reactants were recovered unchanged, whereas the symbol † indicates that decomposition products predominated.

Diene	Dienophile	Solvent	Solvent volume (ml)	Reaction time (days)	Result
215	**278**	Dioxan Δ	20	4	Fail *
229	**278**	Dioxan Δ	20	4	Fail *
227	**278**	Dioxan Δ	20	4	Fail †
215	**220**	PhNO$_2$ Δ	15	7	Fail *
215	**274**	PhNO$_2$ Δ	15	7	Fail *
216	**220**	PhNO$_2$ Δ	15	7	Fail *

216	**274**	PhNO₂ Δ	15	7	Fail *
216	**274**	Sand Bath 240 °C	No Solvent	7	Fail *
230	**220**	Dioxan Δ	15	4	Fail *
230	**274**	Dioxan Δ	15	4	Fail *
230	**220**	PhNO₂ Δ	15	4	Fail *
230	**274**	PhNO₂ Δ	10	4	Fail *
229	**274**	Dioxan Δ	15	4	Fail *
229	**220**	PhNO₂ Δ	10	5	Fail *

228	274	Dioxan Δ	15	4	Fail †
228	220	PhNO₂ Δ	15	6	Fail †
227	274	PhNO₂ Δ	10	7	Fail †
227	220	DCM	10	3	Fail †

(Structures in columns 228/227 are bis-1,2,4-triazines bearing SO₂Me; structures in columns 274/220 are bis-acetylenes.)

Diels-Alder reaction of **231** with phenylacetylene **278**
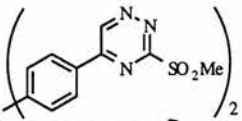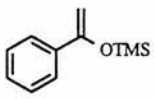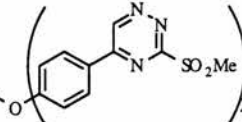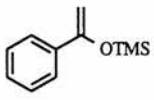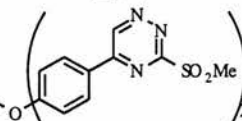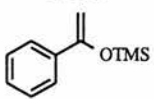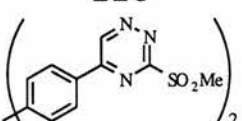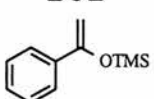
The bis-sulphone 3,3'-bis(methylsulphonyl)-5,5'-bi-1,2,4-triazinyl (0.38 g, 1.19 mmol) was stirred in anhydrous dioxan (20 ml) under nitrogen and phenylacetylene (0.12 g, 1.19 mmol) in anhydrous dioxan (5 ml) was added dropwise with stirring to the reaction mixture. The reaction mixture was then heated under reflux for 48 h under nitrogen, cooled and the solvent evaporated. The residue was extracted with dichloromethane (3 x 30 ml), washed with water (30 ml) and the solvent dried and evaporated. The residue was analysed by NMR and shown to be starting material.
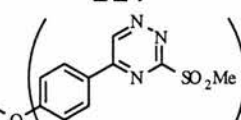
2. General procedure for Diels-Alder reactions with enol ethers

A solution of the bis-1,2,4-triazine (1.19 mmol) and anhydrous solvent was stirred at room temperature under nitrogen and the enol ether (2.36 mmol) was added dropwise with stirring to the reaction mixture. The reaction was heated under reflux with stirring or with stirring at room temperature for the stated time under nitrogen and was

monitored by tlc (ether:petrol 40/60). The solvent was evaporated and the residue extracted with dichloromethane (3 x 25 ml), washed with water (10 ml), dried and the solvent evaporated to dryness. The residue was then analysed by NMR and tlc. The following table describes all combinations carried out. In the table the symbol * indicates that the reactants were recovered unchanged, whereas the symbol † indicates that decomposition products predominated.

Diene	Dienophile	Solvent	Solvent Volume (ml)	Reaction Time (days)	Result
216	**262**	PhNO$_2$ Δ	20	3	Fail *
215	**262**	PhNO$_2$ Δ	15	5	Fail *
230	**262**	Dioxan Δ	25	5	Fail *
230	**262**	PhNO$_2$ Δ	20	5	Fail *
229	**262**	PhNO$_2$ Δ	15	6	Fail *
229	**262**	PhNO$_2$ Δ	10	6	Fail *
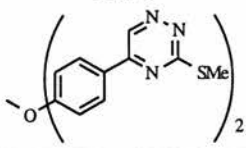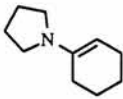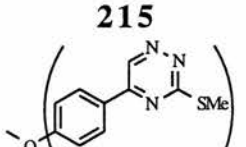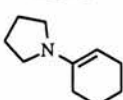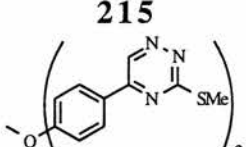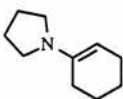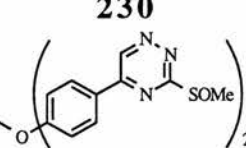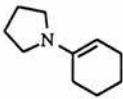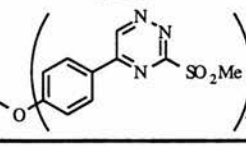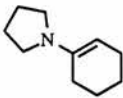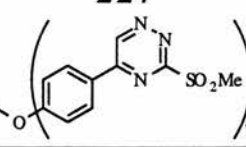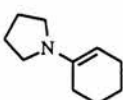
228 (structure)	262 (structure)	Dioxan Δ	20	4	Fail †
227 (structure)	262 (structure)	PhCl Δ	10	3	Fail †
227 (structure)	262 (structure)	Dioxan Δ	15	5	Fail †
228 (structure)	262 (structure)	DCM	10	7	Fail †

3. General procedure for Diels-Alder reactions with mono enamine 1-(1-cyclohexenyl)pyrrolidine

The enamine 1-(1-cyclohexenyl)pyrrolidine was purified by distillation prior to use in all Diels-Alder reaction attempts and was stored under nitrogen at $-28\ ^\circ$C in order to minimise decomposition.

A solution of the bis-1,2,4-triazine (2.88 mmol) and acetic acid (7.20 mmol) in an anhydrous solvent was stirred and the enamine 1-(1-cyclohexenyl)pyrrolidine (1.09 g, 7.14 mmol) in solvent (5 ml) was added dropwise with stirring. The reaction mixture was then heated under reflux with stirring or stirred at 0 $^\circ$C for the described time under nitrogen. The solvent was evaporated and a saturated solution of sodium bicarbonate (20 ml) was added to the reaction mixture. After extraction with dichloromethane (3 x 25 ml) the residue was washed with water (10 ml), dried and the solvent evaporated to dryness. The residue was then analysed by NMR and tlc. The following table describes all combinations carried out. In the table the symbol * indicates that the reactants were recovered unchanged, whereas the symbol † indicates that

decomposition products predominated.

Diene	Dienophile	Solvent	Solvent Volume (ml)	Reaction Time (days)	Result
215	**284**	Dioxan	15	2	Fail *
215	**284**	Dioxan Δ	20	4	Fail *
215	**284**	DCM 0 °C	20	1	Fail *
230	**284**	DCM 0 °C	20	1	Success **287**¶
227	**284**	Dioxan Δ	20	1	Fail †
227	**284**	DCM 0 °C	20	1	Fail *

¶ data for **287** shown below

Preparation of oxy-*p*-phenylenebis-(1-methylsulphinyl-5,6,7,8-tetrahydroisoquinoline **287**

The general procedure was followed using 3,3'-di(methylsulphinyl)-5,5'-(oxydi-

p-phenylene)di-1,2,4-triazine (1.21 g, 2.88 mmol) to give a brown oil which was partially purified by column chromatography (silica gel, ether:petrol 1:1, rf 0.6) and the resultant solid reprecipitated from ethanol to afford oxy-*p*-phenylenebis-(1-methylsulphinyl-5,6,7,8-tetrahydroisoquinoline (0.16 g, 10%) as an orange powder, m.p. 129–131 °C; δ_H 1.67–1.85 (8 H, m, 4 CH$_2$), 2.01–2.16 (8 H, m, 4 CH$_2$), 3.01 (6 H, s, 2 CH$_3$), 7.16 and 8.17 (8 H, AA'BB', Ar-H) and 9.01 (2 H, s); δ_C 23.8 (2 CH$_2$), 24.3 (2 CH$_2$), 25.5 (2 CH$_2$), 29.7 (2 CH$_2$), 40 5 (2 CH$_3$), 120.3 (4 CH, C-2',6'), 128.2 (2 4^{ry}), 128.3 (2 4^{ry}), 128.5 (2 4^{ry}), 129.2 (4 CH, C-3',5'), 130.3 (2 4^{ry}, C-4'), 135.6 (2 CH, C-5), 157.6 (2 4^{ry}, C-1') and 159.5 (2 4^{ry}, C-2); *m/z* 556 (M+, 4%), 527 (32), 466 (64), 403 (43), 342 (32), 218 (100), 189 (36), 118 (11) and 96 (54).

In situ Diels-Alder reaction of 3,3'-di(methylsulphanyl)-5,5'-(oxydi-*p*-phenylene)di-1,2,4-triazine 215 with 1-(1-cyclohexenyl)pyrrolidine 284

3,3'-di(methylsulphanyl)-5,5'-(oxydi-*p*-phenylene)di-1,2,4-triazine (0.5 g, 1.19 mmol) was stirred in anhydrous dichloromethane (20 ml) and *m*-chloroperbenzoic acid (0.44 g, 2.54 mmol, 2.13 equiv.) was added portionwise to the reaction mixture with stirring at 0 °C. The reaction mixture was then stirred at room temperature for 12 h, the solvent evaporated and the solvent changed to anhydrous dioxan (20 ml). The enamine, 1-(1-cyclohexenyl)pyrrolidine (0.45 g, 2.95 mmol), in anhydrous dioxan (15 ml) was then added dropwise to the reaction mixture and the reaction mixture was heated under reflux for 3 days under nitrogen. The solvent was evaporated and the residue stirred in water (10 ml) and extracted with dichloromethane (3 x 20 ml), dried and the solvent evaporated to give a powder which was shown by NMR to be starting materials.

4. *In Situ* bis-enamine formation and attempted Diels-Alder reaction

A solution of 2,2'-terephthaldiylidenedicyclohexanone (1.00 g, 3.40 mmol) in

anhydrous toluene (35 ml) was stirred at room temperature and pyrolidine (2.1 eq.) in anhydrous toluene (10 ml) was added dropwise to the reaction mixture with stirring under nitrogen. 4Å Molecular sieves were present in the reaction mixture in order to actively remove water. The reaction mixture was continued stirring with warming to 50 °C for 5 h under nitrogen, the excess pyrolidine evaporated and 3,3'-di(methylsulphonyl)-5,5'-(oxydi-p-phenylene)di-1,2,4-triazine (1.64 g, 3.40 mmol) in toluene (30 ml) added dropwise with stirring. The reaction mixture was heated under reflux under nitrogen with stirring for 2 days and the solvent evaporated. No cycloaddition product was obtained (from NMR and mass spectrometry evidence).

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Appendix

Table 1. Bis-glyoxals obtained by oxidation of diacetyl-aromatics using DMSO/HBr

Compd. no.	Yield (%)	M.p.(dec.)(°C) (lit. m.p.)	ν_{max} (C=O)	$CH(OH)_2$	OH	^{1}H chemical shifts (δ_H, d_6-DMSO) H-2/H-6	H-3/H-5
209	18	150–156 (160–162)[88] (110–111)[104] (144–147)[117]	1687	5.71	3.60	——8.28s——	
15	59	141–144 (140.5–142)[9] (124–127)[117]	1686	5.71	6.20	8.17	7.15
207	66	135–136 (138–139)[128]	1685	5.68	3.50	8.15*	8.08*
210	91	154–157 (150)[117]	1685	5.74	6.84	8.20	7.92
212	84	133–135§	1687	5.86	6.82	——†——	
211	60	85–89¥	1686	5.70	6.82	-----‡-----	
208	61	92–98¶	1685	5.70	3.55	8.21*	8.10*

* Provisional assignments.

† δ_H 7.89 (2H, d, J 9.0 Hz, H-4 and 6), 8.35 (2H, dd, J 9.0 and 2.0 Hz, H-3 and 7), and 9.01 (2H, d, J 2.0 Hz, H-1 and 9); δ_C(d_6-DMSO) 89.0 [$CH(OH)_2$], 111.9 (C-4 and 6), 123.3 (C-9a and 9b), 123.5 (C-1 and 9), 129.6 (C-2 and 8), 129.8 (C-3 and 7), 158.7 (C-4a and 5a$^\prime$), and 195.3 (C=O).

‡ δ_H 7.54 (2H, d, J 8.0 Hz, H-4 and 6), 8.17 (2H, dd, J 8.0 and 2.0 Hz, H-3 and 7), and 8.48 (2H, d, J 2.0 Hz, H-1 and 9); δ_C(d_6-DMSO) 89.2 [$CH(OH)_2$], 119.8 (C-4 and 6), 121.8 (C-9a and 9b), 125.3 (C-1 and 9), 128.6 (C-2 and 8), 129.9 (C-3 and 7), 147.3 (C-4a and 5a), and 196.0 (C=O).

§ Found: C, 60.7; H, 3.5. $C_{16}H_8O_5 \cdot 2H_2O$ requires C, 60.8; H, 3.8%.

¶ (Found: M$^+$, 350.0476. $C_{16}H_{14}O_7S$ requires M, 350.0477), impurity present, probably **207**

¥ (Found: M$^+$, 332.0369. $C_{16}H_{12}O_6S$ requires M, 332.0371).

Table 2. Bis-[3-(methylsulphanyl)-1,2,4-triazines]

Compd. no.	Yield (%)	M.p. (°C) (from ethanol)	Molecular formula	Found (%) C	H	N	Required (%) C	H	N	m/z M+ (intensity, %)
219	21	246–248 (dec)	$C_{14}H_{12}N_6S_2$	50.95	3.4	25.2	51.2	3.7	25.6	328 (13)
215	31	186–188	$C_{20}H_{16}N_6OS_2$	57.1	3.6	20.0	57.1	3.8	20.0	420 (25)
213	26	223–224	$C_{20}H_{16}N_6O_2S_3$	51.15	3.2	17.6	51.3	3.4	17.9	468 (21)
216	24	243–245	$C_{20}H_{16}N_6S_2$	59.25	3.9	20.6	59.4	4.0	20.8	404 (12)
218	40	289–291(d)	$C_{20}H_{14}N_6OS_2$	57.1	3.3	19.8	57.4	3.3	20.1	418 (3)
217	32	170–172	$C_{20}H_{14}N_6S_3$		†		55.3	3.25	19.3	434 (22)
214	20	205–207	$C_{20}H_{16}N_6OS_3$		‡		53.1	3.6	18.6	452 (7)

† (Found: M+, 434.0431. $C_{20}H_{14}N_6S_3$ requires M, 434.0442), impurity present, unknown.

‡ (Found: M+, 452.0539. $C_{20}H_{16}N_6OS_3$ requires M, 452.0548), impurity present, probably **213**.

Table 3. NMR. spectra of the bis-[3-(methylsulphanyl)]-1,2,4-triazines]

Compd. no.	¹H chemical shifts (δ_H)				¹³C chemical shifts (δ_C)						
	triazine H-6	benzene H-2/H-6	benzene H-3/H-5	CH₃	triazine ring			benzene ring			
					Me	C-3	C-5	C-6	C-1	C-2/C-6	C-3/C-5	C-4
219	9.46	——8.35s——		2.76	14.0	174.2	153.2	141.8	137.0	----128.5----		137.0
215	9.38	8.22	7.21	2.72	13.9	173.7	153.6	141.6	160.0	119.8	128.8	129.9
213	9.39	8.16	8.30	2.73	14.0	174.4	152.5	141.7	144.3	128.7*	128.8*	138.3
216	9.41	8.28	7.85	2.74	14.0	173.9	153.9	141.8	143.8	126.9	128.0	133.0
218	9.53	——†——		2.80	14.0	173.8	154.1	141.9	————————†————————			
217	9.40	——‡——		2.70	14.0	173.8	154.4	141.9	————————‡————————			
214	9.39	8.18	8.30	2.80	13.9	174.3	152.8	141.8	144.2	128.9*	128.5*	138.0

† δ_H 7.79 (2H, d, J 9.0 Hz, H-4 and 6), 8.35 (2H, dd, J 9.0 and 2.0 Hz, H-3 and 7), and 8.92 (2H, d, J 2.0 Hz, H-1 and 9).

δ_C 113.1 (C-4 and 6), 121.1 (C-1 and 9), 124.8 (C-9a and 9b), 127.8 (C-3 and 7), 128.9 (C-2 and 8), and 159.4 (C-4a and 5a).

‡ δ_H 7.51 (2H, d, J 8.0 Hz, H-4 and 6), 8.01 (2H, dd, J 8.0 and 2.0 Hz, H-3 and 7), and 8.15 (2H, d, J 2.0 Hz, H-1 and 9).

δ_C 120.8 (C-4 and 6), 122.0 (C-1 and 9), 124.8 (C-9a and 9b), 127.6 (C-3 and 7), 129.3 (C-2 and 8), and 148.9 (C-4a and 5a).

* provisional assignments

Table 4. Bis-[3-(methylsulphinyl)-1,2,4-triazines] and bis-[3-(methylsulphonyl)-1,2,4-triazines]

Compd. no.	reaction time (h)	Yield (%)	M.p. (dec.)	Molecular formula and H.R.M.S.
230	12	52	108–110	(Found: M^+, 452.0751. $C_{20}H_{16}N_6S_2O_3$ requires M, 452.0758)
229	12	72	135–137	(Found: M^+, 436.0803. $C_{20}H_{16}N_6S_2O_2$ requires M, 436.0809)
227	3	62	208–211*	(Found: M^+, 484.0647. $C_{20}H_{16}N_6S_2O_5$ requires M, 484.0659)
228	5	77	80*	†

* *N.B.* Decompose prior to melting; **Bb** ≥ 100°C and **Bf** ≥ 80°C.
† decomposed on attempted purification by column chromatography.

Table 5. NMR spectra of the bis-[3-(methylsulphinyl)-1,2,4-triazines] and the bis-[3-(methylsulphonyl)-1,2,4-triazines] in d⁶-DMSO

Compd. no.	¹H chemical shifts (δ_H)				¹³C chemical shifts (δ_C)							
	triazine H-6	aromatic H-2/H-6	aromatic H-3/H-5	Me	triazine ring C-3	C-5	C-6	Me	C-1	benzene ring C-2/C-6	C-3/C-5	C-4
230	10.28	8.12	8.58	3.12	173.4	156.0	148.9	39.6	166.1	121.6	128.0	130.0
229	10.38	8.08	8.42	3.16	173.4	153.8	148.9	39.7	143.4	128.0	129.3	132.3
227	10.47	8.13	8.60	3.66	166.0	155.9	148.7	39.6	163.6	119.4	128.7	128.9
228	10.43	8.18	8.32	3.60	166.1	152.9	147.8	39.6	143.2	127.3	128.1	127.5