GENERATION OF 1,3-DIPOLES CONTAINING CARBON, NITROGEN, SULPHUR AND PHOSPHORUS

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Generation of 1,3-Dipoles

Containing Carbon, Nitrogen, Sulphur and Phosphorus

by

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Abstract

Most of the known 1,3-dipoles of propargyl-allenyl type ($A{\equiv}B^{-}{-}C^{-}$) are composed of carbon, nitrogen and oxygen. Very few 1,3-dipoles of this type contain atoms from the third or lower periods. The nitrile sulphide ($R{-}C{\equiv}N^{-}{-}S^{-}$), a recently discovered family of 1,3-dipoles, incorporates sulphur in its π manifold. Our attempts to isolate this very reactive intermediate proved that a bulky group, adamantyl ($C_{10}H_{15}$-), could not appreciably stabilize it.

Our synthesis of the bis(nitrile sulphides) or their *synthetic equivalents* started with the adamantyl (1,3-$C_{10}H_{14}$-) substituent. 1,3-Bis(1',3',4'-oxathiazol-2'-one-5'-yl)-adamantane **3-28a**, the precursor for the 1,3-bis(nitrile sulphide)-adamantane **3-20a**, was prepared and its cycloaddition reactions to DMAD and 1,3-bis(cyano)adamantane were examined. It was found that the bis(nitrile sulphide) **3-20a** had a comparable reactivity to that of adamantyl nitrile sulphide **2-6**. 1,8-Bis(1',3',4'-oxathiazol-2'-one-5'-yl)-octane **3-28b**, another precursor for bis(nitrile sulphide) **3-20b**, was also prepared but others such as 1,1-bis(1',3',4'-oxathiazol-2'-one-5'-yl)-methane **3-28c** and 1,4-bis(1',3',4'-oxathiazol-2'-one-5'-yl)-benzene **3-28d** could not be synthesized from similar reactions of the corresponding amides with ClSC(O)Cl due to the strong hydrogen bonding existing in the amides. The conjugated phenyl isothiazolyl oxathiazolones **3-41** and **3-42** were synthesized and their cycloaddition reactions to dipolarophiles were examined. The

possibility of producing the poly(isothiazoles) from these oxathiazolones will be discussed.

A novel synthetic route to the precursor, 1,3,4-oxathiazol-2-one, has been discovered. A better starting material, *N,O*-bis(trimethylsilyl)carbonamide **4-7**, was used to replace the amide in the reaction to avoid the strong hydrogen bonding. Several oxathiazolones such as 5-methyl-1,3,4-oxathiazol-2-one **4-4a**, 5-(4'-biphenyl)-1,3,4-oxathiazol-2-one **4-4c**, 1,4-bis(1',3',4'-oxathiazol-2'-one-5'-yl)-benzene **4-4d** and 4,4'-biphenyl-bis(1",3",4"-oxathiazol-2"-ones) **4-4e** were prepared through the new route.

The reactions of amides **5-21** with ClSC(O)Cl were proposed to synthesize the heterocycles **5-22** which were supposed to be the precursors to the new 1,3-dipoles **5-23**. The reactions of *p*-toluenesulfinamide/*N,N*-bis(trimethylsilyl)-*p*-toluenesulfinamide **5-24** with ClSC(O)Cl did not give the expected precursor **5-22** but *p*-toluenedisulfide **5-25**, *p*-toluenethiol-*p*-toluenesulfonate **5-26** and cyanuric acid **5-27**. Benzenesulfonamide/*p*-toluenesulfonamide with ClSC(O)Cl did not give any product but the amides themselves. A new reaction of adamantyl phosphaalkyne **5-37** with elemental sulphur with or without Et_3N present in toluene was tested for the synthesis of phosphaalkyne sulphide **5-38**.

Acknowledgements

This thesis would never have been finished without the following people and I am greatly indebted to them: my supervisor, Dr. Melbourne J. Schriver, for his guidance; my wife, Li Jin, and my son, Yixin Zhu, for their understanding and encouragement; my parents and my parents-in-law for their continuous support.

My sincere thanks to the following people: Dr. C. R. Lucas and Dr. G. J. Bodwell (for proofreading), Dr. M. Regitz, Dr. D. J. Burnell and Dr. J. Bestari (for their helpful discussions), Dr. J. N. Bridson (for X-ray crystallography), Steve Copp and Cheryl Morgan (for friendship), Neil Squires (for some experiments), Dr. C. R. Jablonski and N. Brunet (for NMR spectra), D. Miller (for NMR spectra and X-ray crystallography), Dr. B. Gregory and M. Baggs (for mass spectra), the department secretaries (for too many services to list).

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Glossary of Abbreviations

Ac	acetyl
Anal	elemental analysis
Å	angstrom (= 10^{-8} cm)
Ar	aromatic substituent
aro	aromatic
b.p.	boiling point
Bu	butyl
Bz	benzoyl
Calcd	calculated
[CCCNS]	isothiazole ring
[COCOSN]	oxathiazolone ring
d	doublet
D	bond distance
dec	decomposed
DMAD	dimethylacetylenedicarboxylate
DMSO	dimethylsulfoxide
Ed	editor
Et	ethyl

FT-IR	fourier transform infrared spectroscopy
het	heterocyclic
HOMO	highest occupied molecular orbital
hr	hour
IR	infrared spectroscopy
LUMO	lowest unoccupied molecular orbital
m	medium (for IR) or multiplet (for NMR)
M	molecular fragment
Me	methyl
Mesityl	2,4,6-trimethylphenyl
min	minute
MO	molecular orbital
m.p.	melting point
ms	medium strong
MS	mass spectrometry
m/z	mass/charge
NMR	nuclear magnetic resonance spectroscopy
ORTEP	Oakridge Thermal Ellipsoid Program
Ph	phenyl
ppm	parts per million

q	quartet
quat	quaternary
ref.	reference
s	strong (for IR) or singlet (for NMR)
sh	shoulder
Super mesityl	2,4,6-tri(*t*-butyl)phenyl
t	triplet
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane
UV	ultraviolet spectroscopy
UV-vis	ultraviolet-visible spectroscopy
vdW	average van der Waals' distance
w	weak

To Jenny and Yixin

Chapter 1

General Introduction

1.1 1,3-Dipoles

Cycloaddition reactions have provided the most effective way towards heterocycles. There are many different types of cycloaddition reactions such as [4+2] (a combination of a 4-centre-π-electron system with a 2-centre-π-electron system), [2+2+2] (a combination of three 2-centre-π-electron systems), [3+3] (a combination of two 3-centre-π-electron systems), and [3+2] (a combination of a 3-centre-π-electron system with a 2-centre-π-electron system). Some of the [3÷2] cycloadditions are 1,3-dipolar cycloaddition processes[1] in which a 1,3-dipole (3-centre-nπ-electron species having zwitterionic octet structures) is the diene.

Although the 1,3-dipolar cycloaddition reaction was initially defined in terms of the allyl type (a 2π electron system) of π-systems[1] (Figure 1-1), there are two different types of

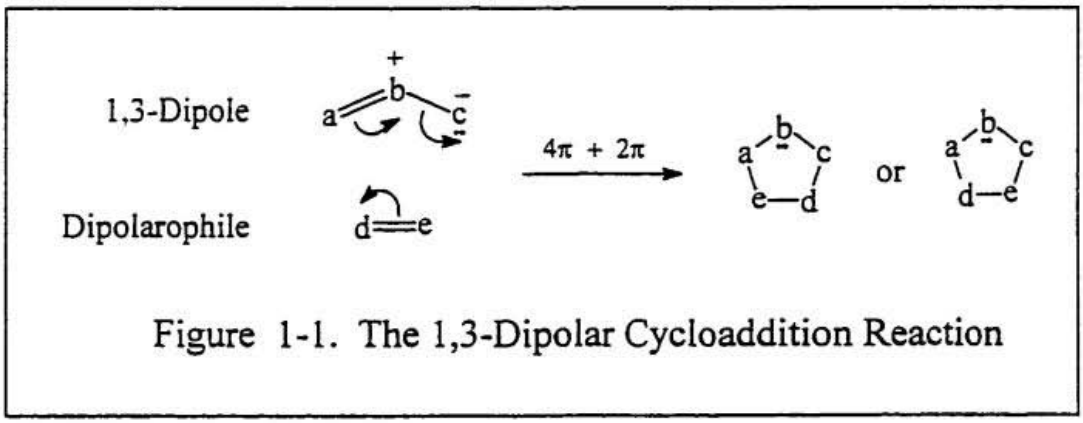


Figure 1-1. The 1,3-Dipolar Cycloaddition Reaction

1,3-dipole, that is, the allyl and the propargyl-allenyl (a 4π electron system). As represented in Figure 1-1, the important difference between the allyl anion and the 1,3-dipoles of the allyl type is that the centre atom of the 1,3-dipole bears a formal charge and can accommodate a

lone pair of electrons after the ring closure. It is sometimes confusing to use the term polarity to describe the 1,3-dipoles unless the detailed structures are considered. The dipole moments of the bent shapes (the allyl type) are detectable whereas those of the linear structures (the propargyl-allenyl type) may not be detectable when one terminal atom *a* is identical to the other *c* (Figure 1-2).

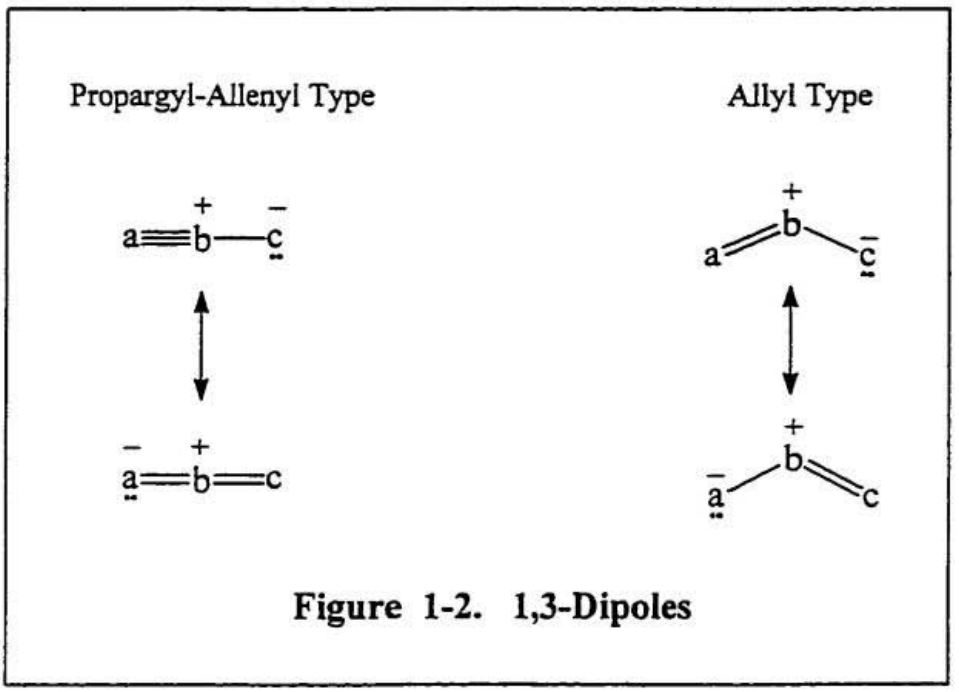


Figure 1-2. 1,3-Dipoles

The mechanism of the 1,3-dipolar cycloaddition reactions was first proposed by Huisgen[2] to be a concerted process, as it is in most other cycloaddition reactions (e.g. 1,4-addition of an alkene to a conjugated diene). This has now been widely accepted. There is, however, another alternative: a two step 1,3-dipolar cycloaddition process which would lead to the zwitterion[3] or the biradical[4] intermediates. The arguments for the alternative are based

on Sustmann's molecular orbital perturbation theory[5] which can be simply illustrated by using the frontier π-MO's of the 1,3-dipole , the transition state of the cycloaddition, and the dipolarophile (Figure 1-3). There are two sets of HOMO-LUMO pairs. When the energy

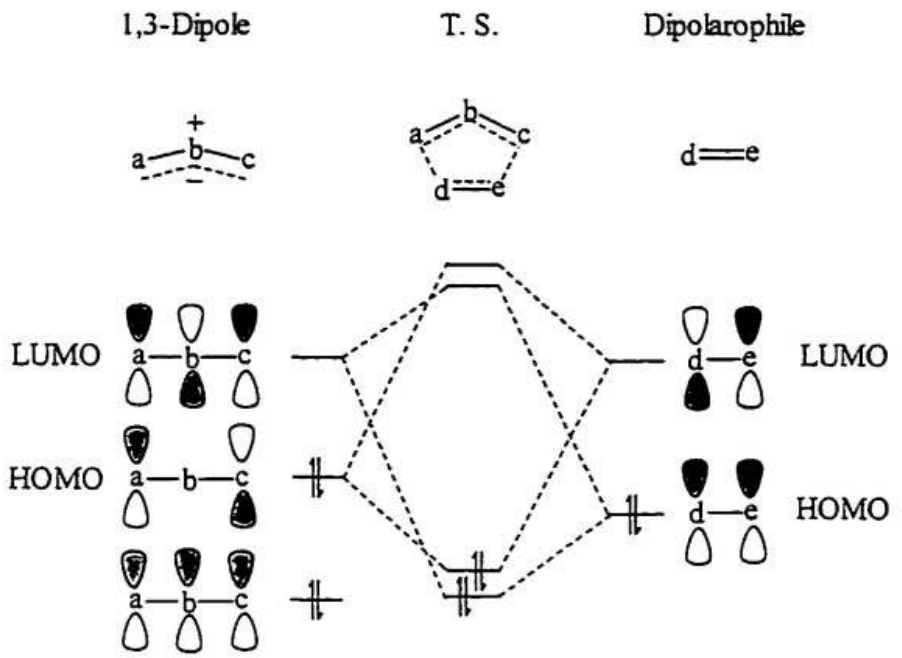


Figure 1-3. The Frontier π MO's of 1,3-Dipolar Cycloaddition

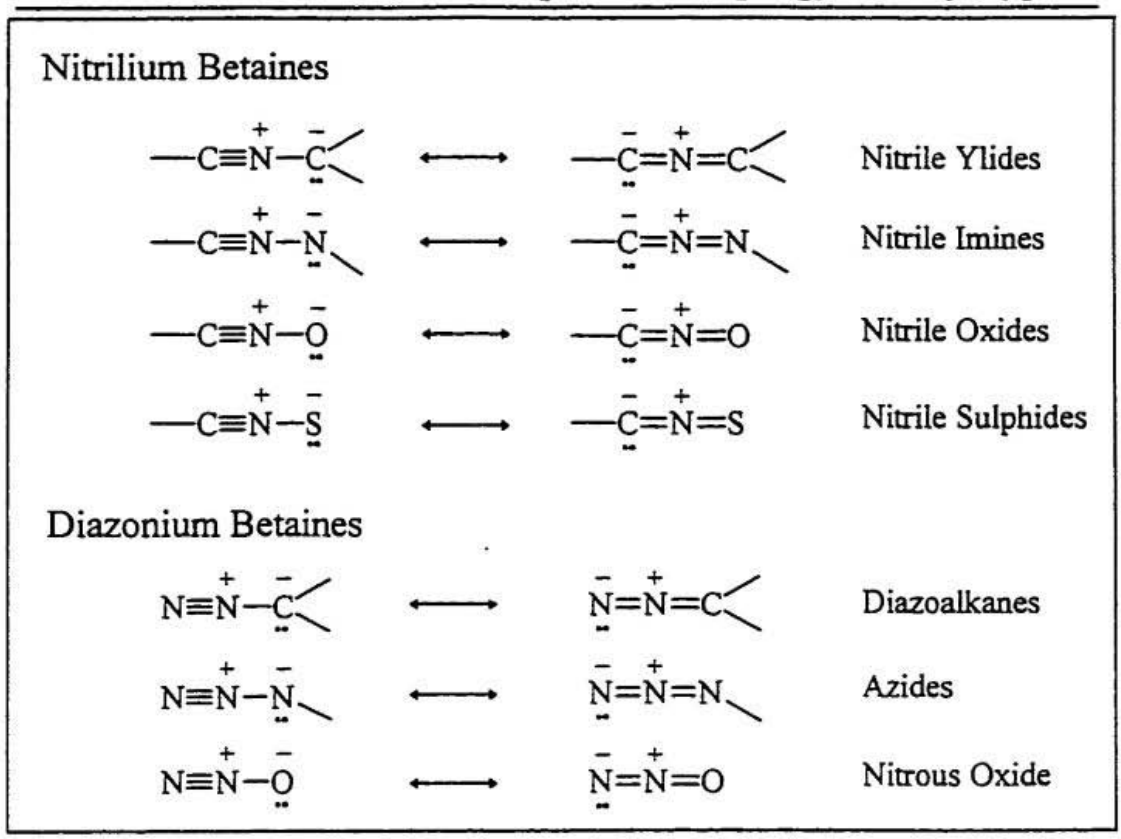
gap between one pair of the HOMO-LUMO is much smaller than the other pair, the electron flow would be unidirectional in a concerted process. Otherwise the electron flow would be two-directional: from HOMO (1,3-dipole) to LUMO (dipolarophile) and back from HOMO (dipolarophile) to LUMO (1,3-dipole) to form the two new σ-bonds. The two step

cycloaddition process will take place only under one of the following conditions: either the atomic coefficient at one end of the 1,3-dipole is much smaller than at the other or a strong steric hindrance exists at one end of the 1,3-dipole[6]. The reactivity[5] and regioselectivity[6] in 1,3-dipolar cycloaddition reactions can also be approached by using Figure 1-3. In order to reduce the HOMO-LUMO energy gap, one of the strategies is to introduce electron-withdrawing groups into either the 1,3-dipole or the dipolarophile. Since the 1,3-dipoles of the propargyl-allenyl type, which are the interests of this work, are electron rich (3-centre-4π-electron) species, the cycloaddition reactions between these 1,3-dipoles and the dipolarophiles will be more favourable to those dipolarophiles that are attached by electron withdrawing groups. The term "activated by electron withdrawing groups" which is used later in the thesis refers to the fact that the LUMO energy level is lowered and the HOMO-LUMO energy gap is then reduced.

1.2 New 1,3-Dipoles of Propargyl-Allenyl Type

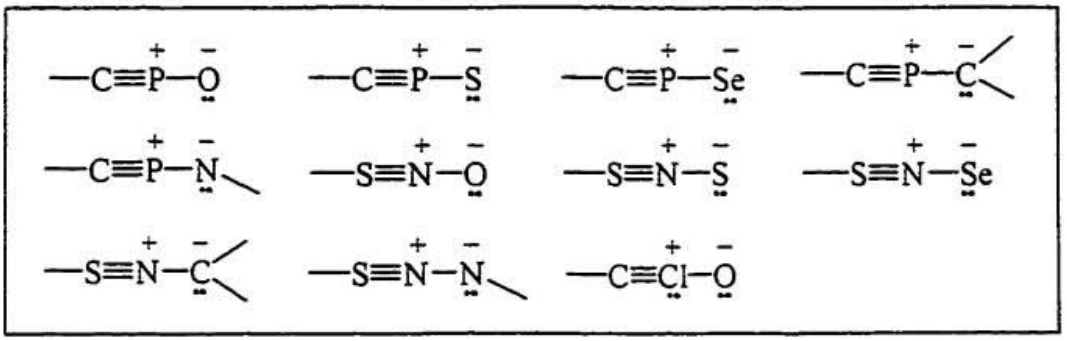
The known 1,3-dipoles of propargyl-allenyl type are listed in Table 1-1. From the Table, it is clear that known 1,3-dipoles of the propargyl-allenyl type are usually composed of C, N, and O. A few 1,3-dipoles are featured with other atoms. Moreover, Huisgen pointed out[1] that the central atom *b* of 1,3-dipoles of this type should only be one of the Group V elements which would bear a positive charge in the quatervalent state. In general this is correct, however, in some unusual cases, however, Group VII elements could also replace the central position of the 1,3-dipole without breaking any chemical principles. An example of this would be $-C{\equiv}Cl^{+}-O^{-}$ (Table 1-2), if it could be generated. So far only N has

Table 1-1. The Known 1,3-Dipoles of Propargyl-Alleny Type



been used as the central atom for all the known 1,3-dipoles of this type. The number of the 1,3-dipoles is still very limited as well because of the limited selection of elements (mostly C, N, O). The limitation comes from the 1,3-dipole itself. These 1,3-dipoles are mostly thermodynamically unstable species compared to their decomposition products or cycloaddition products. They may be, however, isolable (kinetically stable) under normal conditions (e.g. room temperature and ambient pressure) when bulky substituents are attached. Carbon, nitrogen and oxygen are small atoms in size and have high/moderate

Table 1-2 Some Unknown 1,3-Dipoles of Propargyl-Allenyl Type



electronegativities so that they usually can form strong σ and π bonds. Therefore 1,3-dipoles of the propargyl-allenyl type composed of these three atoms are more stable than those formed by other atoms. This does not mean that 1,3-dipoles of this type can not be generated from other elements. It may, however, imply that more technical protections are required in order to generate 1,3-dipoles containing other elements, especially those with large sizes. Some of these unknown 1,3-dipoles of the propargyl-allenyl type are proposed in Table 1-2. A major goal of this research was to examine the possibility of novel 1,3-dipoles composed of other elements especially the heavier *p* block elements (such as S, P, Se, As, etc.). This is of great interest not only for the synthesis of novel 1,3-dipoles but also for the chemistry of the unsaturated π-bonding between the *p* block elements from different periods that should result. For example, replacing the nitrogen atom in a nitrile oxide (Table 1) with a phosphorus atom would give a new species, (a phosphaalkyne oxide). Would it be a 1,3-dipole ($R\text{-}C{\equiv}P^{+}\text{-}O^{-}$) just like its nitrogen (no d orbitals available for more bonding, octet rule) derivative or would it prefer a phosphorus(V) compound (R-C≡P=O, d orbitals available for phosphorus)? If the latter is true, what would be the bonding model for this kind of

compound containing three π-bonds at one atom? Other unknown species such as R-C≡P^{+}-S^{-}, R-C≡P^{+}-Se^{-}, R-S≡P^{+}-O^{-}, R-S≡P^{+}-S^{-}, R-S≡N^{+}-S^{-}, R-S(O)≡N^{+}-S^{-} (see Table 1-2) and many more would also raise the latter issue.

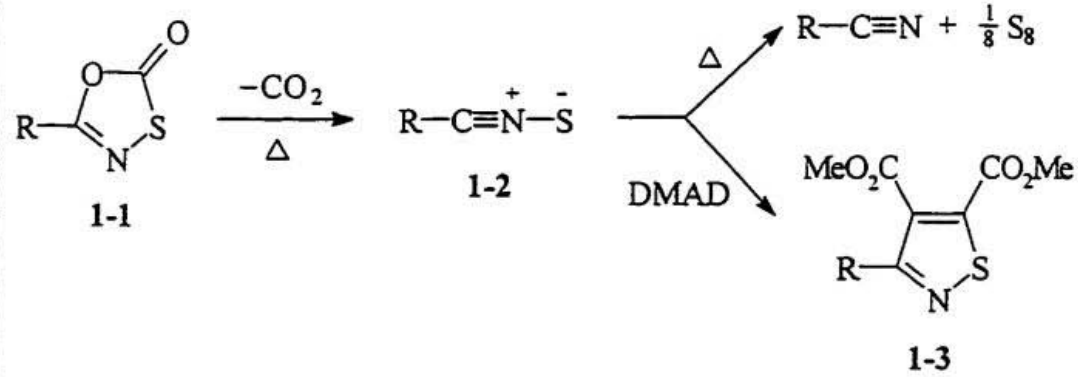
The consequence of substituting heavy elements for light (second period) elements would be the instability of the new 1,3-dipoles since a 3pπ-2pπ bond or a 3pπ-3pπ bond will be much weaker than a 2pπ-2pπ bond. It is therefore impossible to isolate thermodynamically stable 1,3-dipoles of this type and it is necessary to use some techniques to stabilize them (kinetic stabilization) such as low temperature reactions, trapping and bulky substituent. The weak bonding between the heavy elements or between a heavy element and a light element will also behave differently although they do have π-bonding characters. For instance, phosphanitriles (RR'P≡N, R,R' = bulky substituent) contain P≡N triple bond character but sometimes they may react as nitrenes[71].

The nitrile sulphides[7] (R-C≡N^{+}-S^{-}), a recently discovered family of 1,3-dipoles, were selected as the starting point for this work and the replacement of C with S and S=O and of N with P in the nitrile sulphide was examined by several methods.

1.3 The Nitrile Sulphides

The nitrile sulphides (**1-2**) were first proposed as thermally unstable intermediates from the decomposition of 5-substituted-1,3,4-oxathiazol-2-ones (**1-1**) by Franz and Black[8] in 1970. Actually Senning had reported earlier that the oxathiazolone heterocycle could give a nitrile R-C≡N, S_8, and CO_2 upon heating[9]. When Franz and Black repeated the reaction

in the presence of dimethylacetylenedicarboxylate (DMAD), a dipolarophile, the [3+2]



Scheme 1-4. Generation, decomposition, and cycloaddition of nitrile sulphides

cycloadduct isothiazole (**1-3**) was isolated (Scheme 1-4). In the absence of the dipolarophile, the unstable nitrile sulphide decomposed to give the nitrile and elemental sulphur. Since then intensive studies on nitrile sulphides have been carried out[10-32]. The only direct evidence for the existence of a nitrile sulphide so far was provided by Holm and coworkers[10] in 1975. They irradiated 5-phenyl-1,3,4-oxathiazol-2-one in an ether-isopentane-ethanol glass at -180°C and found a UV absorption at 335 nm which disappeared only when the matrix melted at -133°C. The absorption was assigned to benzonitrile sulphide.

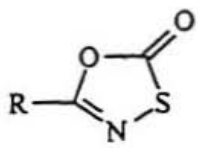
1.3.1 Precursors

As described in the review by Paton[7], several routes can be followed to generate nitrile sulphides. They are thermal decomposition, photochemical decomposition, and miscellaneous reactions. The thermal decomposition method is the most common one because it is a more efficient process and the precursors are easier to handle than in the other

routes. No matter which method is used, nitrile sulphides are so unstable that precursors to generate them *in situ* are essential. Compounds **1-1**, and **1-4** to **1-19** can be used to generate nitrile sulphides by eliminating small molecules such as CO_2, CS_2, SCO, N_2, and RC≡N under certain conditions. Among these precursors, 1,3,4-oxathiazol-2-ones **1-1** are the best to generate nitrile sulphides under mild conditions and to give very convenient access to this kind of compound. A more detailed discussion about oxathiazolones will be given in Chapter 4.

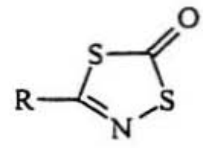
1.3.2 Generation

Since nitrile sulphides are very unstable species, they have to be generated from precursors and trapped *in situ* by dipolarophiles to form heterocycles which contain the C=N-S moiety. For thermal generation of nitrile sulphides, the precursors and the dipolarophiles are dissolved in a solvent and then heated to certain temperatures (for example, 130-165°C for 1,3,4-oxathiazol-2-ones with dimethyl acetylenedicarboxylate in toluene) to carry out the generation as well as the cycloaddition. The criteria for choosing a solvent for these reactions are its boiling point and inertness toward the reactants. The solubilities of the precursor, the dipole, and the dipolarophile in the solvent are also important for the reactions. The principle of generating nitrile sulphides photochemically is basically the same as that for the thermal reactions. The mechanism for the photochemical reactions, however, could be different from that of the thermal reactions. Although a clear mechanism has not been reported, it is generally believed, based on spectroscopic evidence[27], that the unstable 4π-antiaromatic thiazirine (CNS 3-member ring) was formed first and then rearranged to the



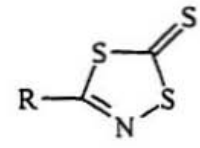
1-1

1,3,4-oxathiazol-2-one



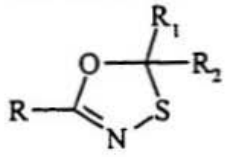
1-4

1,4,2-dithiazol-5-one



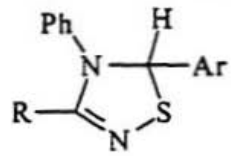
1-5

1,4,2-dithiazol-5-thione



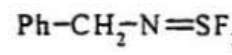
1-6

1,3,4-oxathiazole



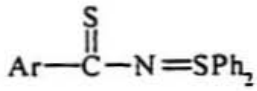
1-7

4,5-dihydro-1,2,4-thiadiazole



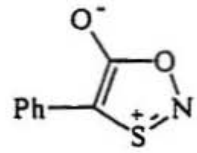
1-8

(benzylimino)sulphur difluoride



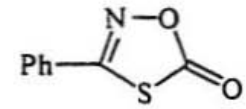
1-9

N-thioacyl diphenylsulphinimides



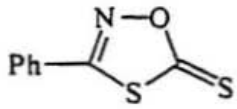
1-10

mesoionic oxathiazolone



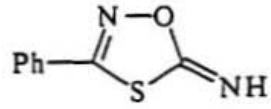
1-11

1,3,4-thioxazol-2-one



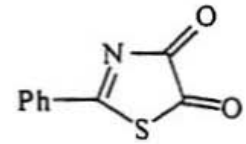
1-12

1,3,4-thioxazol-2-thione



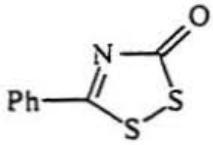
1-13

1,3,4-thioxazol-2-imine



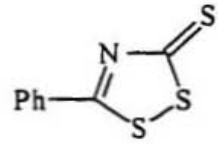
1-14

1,4-thiazol-2,3-dione



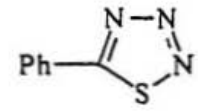
1-15

1,2,4-dithiazol-3-one



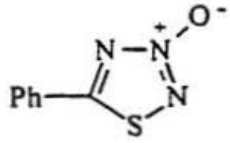
1-16

1,2,4-dithiazol-3-thione



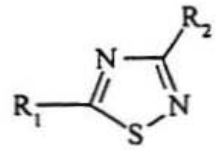
1-17

1,2,3,4-thiatriazole



1-18

1,2,3,4-thiatriazol-3-oxide



1-19

1,2,4-thiadiazole

corresponding nitrile sulphide[7].

1.3.3 Cycloadditions

As unstable electron rich 1,3-dipoles, the nitrile sulphides have been found to have only two chemical reactions, decomposition and addition. Nitrile sulphides have been shown to decompose to the corresponding nitrile and elemental sulphur very rapidly as soon as they are generated. Nitrile oxides[1] ($R\text{-}C{\equiv}N^{+}\text{-}O^{-}$), the oxygen derivatives of nitrile sulphides, can be isolated in the presence of sterically protective groups such as mesityl (2,4,6-trimethylphenyl) or "super mesityl" (2,4,6-tri-*tert*-butylphenyl). Conditions such as excess dipolarophile and low concentration of the nitrile sulphide may allow the cycloaddition reactions between nitrile sulphides and dipolarophiles to compete with the decompositions of the nitrile sulphides which is a bimolecular process. It seems that the cycloaddition reaction is the only currently known way to utilize the nitrile sulphides and is also the general method used to prove the existence of the unstable intermediate 1,3-dipoles.

Nitrile sulphides should react with any unsaturated p system with an appropriate HOMO and LUMO. As electron rich 1,3-dipoles, nitrile sulphides will in fact react efficiently only with electron poor p systems to give the cycloadducts rather than the decomposition products. This may also explain the fact that the established cycloaddition reactions for nitrile sulphides are limited compared to nitrile oxides or ylides or imines (Table 1). The known cycloaddition reactions of the nitrile sulphides are illustrated in Scheme 1-5. The yields of the cycloadducts from these reactions varied from as low as 5%[30] up to near quantitative conversion (96%)[14] due to variations in the stability of the nitrile

sulphide and reactivity of the dipolarophile.

1.3.4 Dipolarophiles

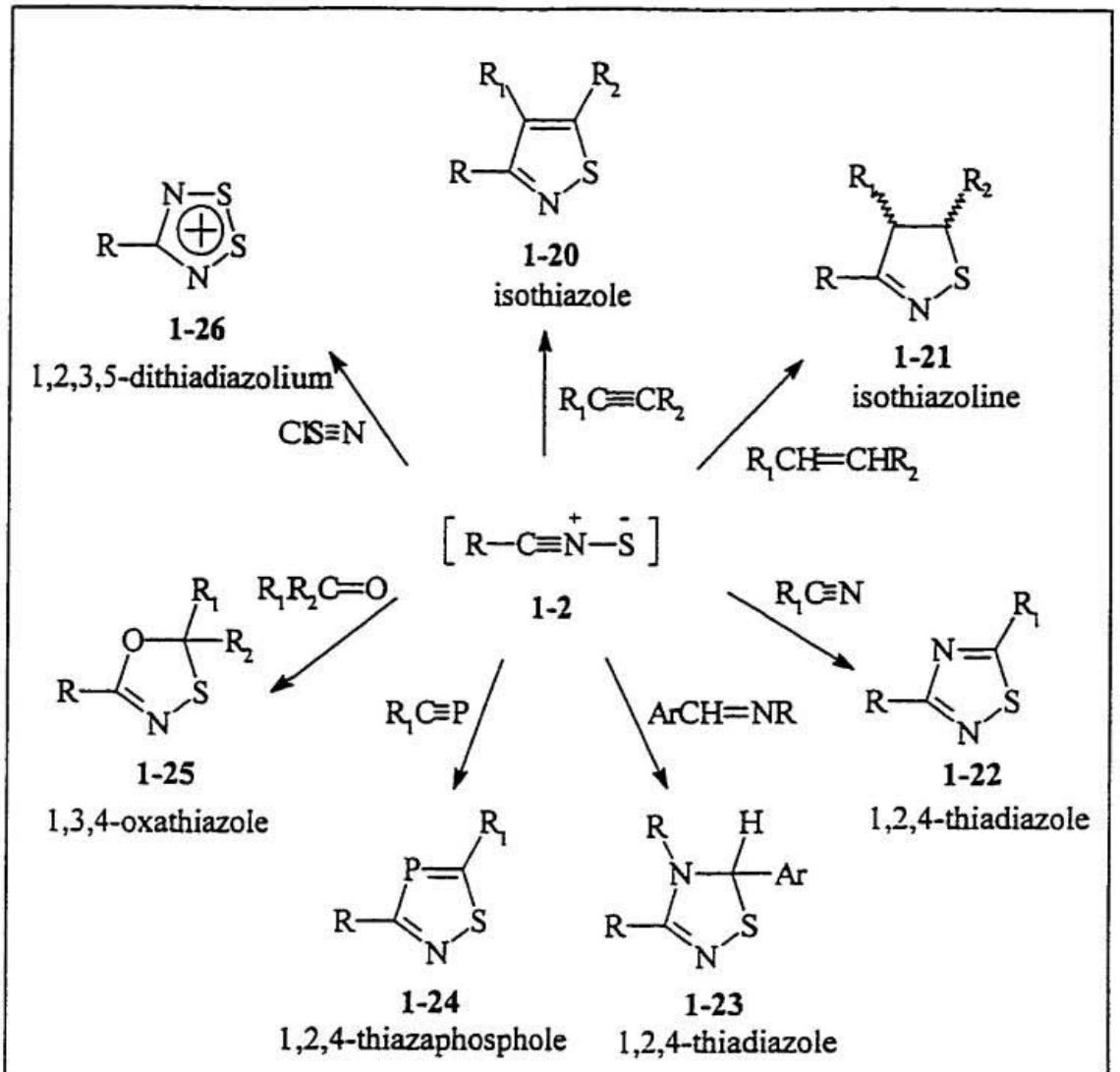
The dipolarophiles which have been used to trap nitrile sulphides in 1,3-dipolar cycloaddition reactions are alkynes/acetylenes, alkenes, nitriles, imines, carbonyl compounds, phosphaalkynes and thiazyl chloride (Scheme 1-5).

1.3.4.1 Alkynes or Acetylenes

The first dipolarophiles that were reported to successfully react with a nitrile sulphide were dimethyl acetylenedicarboxylate (DMAD) and ethyl propiolate[8]. The π bonds (C≡C) in these molecules are very active toward electron rich dipoles like a nitrile sulphide due to the electron withdrawing carbonyl group(s) which lower the energy of the HOMO and LUMO facilitating a cycloaddition reaction. DMAD remains the most widely used dipolarophile for trapping nitrile sulphides due to its two carbonyl groups. Other alkynes and acetylenes such as methyl propiolate[20], 3-butyn-2-one[20], phenylacetylene[32], ethyl 2-butynoate[14], and ethyl phenylpropiolate[14] have also been used to trap nitrile sulphides. The yields of the cycloadducts from these alkynes/acetylenes and nitrile sulphides were not as good as from DMAD. The cycloaddition of a nitrile sulphide with an alkyne/acetylene will produce an aromatic five-membered ring called an isothiazole. Intramolecular 1,3-dipolar cycloadditions between nitrile sulphides and alkynes/acetylenes have been used to make five-membered heterocycles[33].

1.3.4.2 Alkenes

The first alkene used successfully to trap a nitrile sulphide was maleic anhydride[20]



Scheme 1-5. The known cycloaddition reactions of nitrile sulphides

generated from N-benzyliminosulfurdifluoride. A series of alkenes have been studied for the cycloaddition reactions with nitrile sulphides bearing different groups[12, 32, 33-35]. The cycloaddition of nitrile sulphide and alkenes is also the only known method for preparation

of 2-isothiazolines (**1-21**). Some alkenes such as dimethylfumarate[34], diethylfumarate[12], 2,3-dimethyl-2-butene[32], phenyl acrylate[34], norbornene[35], norbornadiene[35], dimethyl 5-norbornene-*cis,endo*-2,3-dicarboxylate[34], N-ethylmaleimide[34], 2-chloroacrylate[34], and b-pyrrolidinylacrylate[34] have high reactivities toward the nitrile sulphides while others such as tetraethyl ethenetetracarboxylate (strong steric effect), b-nitrostyrene and 3-nitrostyrene (insufficient electron withdrawing groups attached) did not react with the nitrile sulphides[34]. The intramolecular 1,3-cycloadditions of the nitrile sulphides and alkenes have also been used[33] to make some fused ring systems such as isothiazolquinolinones, chromenoisothiazolones, and chromenoquinolinones.

1.3.4.3 Nitriles

As mentioned above, nitrile sulphides prefer to react with activated dipolarophiles (attached directly to electron-withdrawing groups). Some nitriles are reactive towards nitrile sulphides even without electron-withdrawing group(s). Only those nitriles which are substituted by electron-withdrawing groups, however, give good yields of the cycloadducts. Ethyl cyanoformate[12,36-38], a-ketonitrile[39,40], and trichloroacetonitrile[41] are the most reactive nitriles. They react with nitrile sulphides to form the 5-substituted 1,2,4-thiadiazoles **1-22** (yields: 50-95%), an important class of heterocycles showing a range of biological activities[42,43]. Ethyl cyanoformate is a particularly good trap for nitrile sulphides not only because it is highly reactive but also because it often affords crystalline adducts that can be easily removed from the reaction mixture (low b.p. *ca.* 115 °C)[7]. The cycloadditions of nitrile sulphides and nitriles have been applied to the synthesis of some natural products such as

dendrodoine[40] and a vibovasin analogue[44].

1.3.4.4 Imines

There is only one report[19] on imines acting as the dipolarophile toward nitrile sulphides. The imines were formed from the condensation of aniline with benzaldehyde, *p*-chlorobenzaldehyde, and *p*-nitrobenzaldehyde, and they were then added to *p*-methoxybenzonitrile sulphide as dipolarophiles to form 4,5-dihydro-1,2,4-thiadiazoles (**1-23**). All these imines have shown very low reactivity toward nitrile sulphides (yields ≤ 13%). The cycloadducts (**1-23**) will also undergo retro-1,3-dipolar cycloaddition to nitrile sulphides and imines upon heating. This reaction has been exploited as a synthetic route to the nitrile sulphides.

1.3.4.5 Carbonyl Compounds

Those carbonyl compounds such as hexachloroacetone, chloral, α,α,α-trifluoroacetophenone[45] and methyl benzoylformate[7], which are activated by electron withdrawing groups can undergo cycloadditions with nitrile sulphides. 1,3,4-Oxathiazoles (**1-25**), the cycloadducts from these reactions, are difficult to synthesize by other means[7]. Like 1,2,4-thiadiazoles (**1-23**), the cycloadducts from the imines, all the oxathiazoles (**1-25**) will go back to nitrile sulphides and the carbonyl compounds upon heating[18].

1.3.4.6 Phosphaalkynes

There are two reports[46,47] on trapping nitrile sulphides by using phosphaalkynes while intensive studies on trapping nitrile oxides by phosphaalkynes[46,48-51] have been carried out. It has been demonstrated that *t*-butylphosphaalkyne (*t*-BuC≡P) is a very strong dipolarophile

towards these two nitrilium betaines not because the phosphaalkyne is activated by electron withdrawing groups but because it is a kinetically stable species and the cycloadduct, 1,2,4-thiazaphosphole (**1-24**), from the reaction is a thermodynamically stable compound. The cycloadduct has never been prepared by other means.

1.3.4.7 Thiazyl Chloride

The only report[52] on thiazyl chloride as a dipolarophile in the cycloaddition reaction of nitrile sulphides was given by this research group. The reaction of adamantyl nitrile sulphide with thiazyl chloride was supposed to give two cationic isomers 1,2,3,5-dithiadiazolium **1-26** and 1,3,2,4-dithiadiazolium. Only one isomer **1-26** was recovered from the reaction in ~50% yield. The reaction was believed to provide a new general route to dithiadiazolium salts and subsequently to the dithiadiazolyl radicals which have potential applications in the preparation of conducting materials.

Chapter 2

The Generation and Cycloaddition of Adamantyl Nitrile Sulphides

2.1 Introduction

2.1.1 The Known Nitrile Sulphides

It has been 26 years since benzonitrile sulphide, the first nitrile sulphide, was discovered. Other known nitrile sulphide derivatives have been generated from different precursors and trapped by different dipolarophiles. There have been reviews on the nitrile sulphide cycloaddition reaction[7,59] but a full, recent survey has not been conducted. Therefore a complete summary of the known nitrile sulphides and their reactions with the dipolarophiles is made in this chapter. Table 2-1 lists all the known nitrile sulphides, the precursors used to generate the 1,3-dipoles, the dipolarophiles, and the yield of the cycloadduct (cycloadducts) in collected form for the first time. There are 54 nitrile sulphides generated from 17 different types of precursor heterocycles and 35 dipolarophiles (except those in the intramolecular cycloadditions) which were employed in the cycloaddition reactions. It is clear from Table 2-1 that most of the known nitrile sulphides are generated from precursors that are directly substituted by aromatic rings. Only eight examples of this 1,3-dipole family attached by saturated substituents are known and the yield of the cycloadducts from those nitrile sulphides are generally much lower than that from the aromatic derivatives. Table 2-1 contains information published up to December 1996 and excludes the information in this thesis or associated publications.

Table 2-1 The Known Nitrile Sulphides

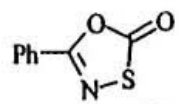
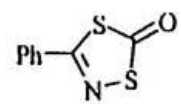
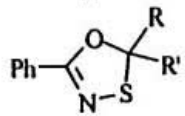
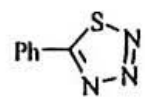
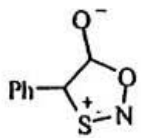
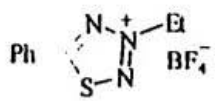
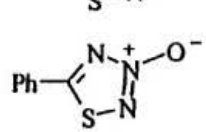
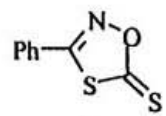
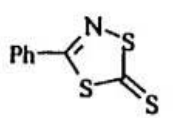
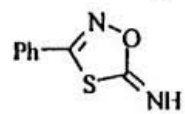
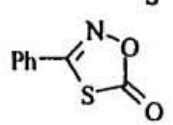
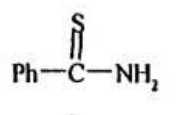
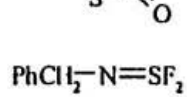
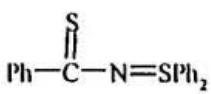
Nitrile Sulphide	Precursor	Dipolarophile	Yield of Cycloadduct(s)	Ref.
Ph—C≡N⁺—S⁻	 	$MeO_2CC{\equiv}CCO_2Me$	5 - 90%	8, 10, 14, 16, 20, 22, 24, 28, 30, 55
		$HC{\equiv}CCO_2Et$	70%, 83%	8, 14
	 	$HC{\equiv}CCO_2Me$	78%	20
		$Ph(O)CC{\equiv}CC(O)Ph$	?%	55
		$t\text{-}BuC{\equiv}P$	82%	50
	 	$EtO_2CC{\equiv}N$	75%, 87.5%	53, 37
		$PhC{\equiv}N$	41%	37
		$Cl_3CC{\equiv}N$	48%	41
	 	$p\text{-}MeC_6H_4C{\equiv}N$	33%	37
		$p\text{-}ClC_6H_4C{\equiv}N$	56%	37
	 	$2\text{-}Cl\text{-}4{,}6\text{-}(NO_2)_2C_6H_2C{\equiv}N$	43%	58
		$2{,}4\text{-}(NO_2)_2C_6H_3C{\equiv}N$	15%	58
	 	$(NC)_2C{=}C(CN)_2$	48 -70%	56
		$PhC{\equiv}CH$	22%	32
		$Me_2C{=}CMe_2$	48 - 52%	32
	 	$trans\text{-}MeO_2CCH{=}CHCO_2Me$	55%	34
		$(Et_2OC)_2C{=}C(CO_2Et)_2$	0%	34
		$C_4H_8N\text{-}CH{=}CHCO_2Et$	< 2%	34

Table 2-1 The Known Nitrile Sulphides (continued)

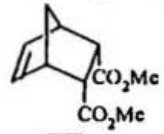
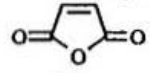
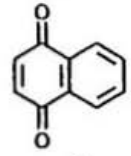
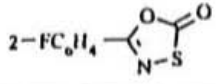
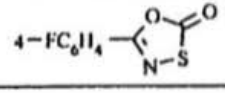
Nitrile Sulphide	Precursor	Dipolarophile	Yield of Cycloadduct(s)	Ref.
PhC≡N⁺–S⁻		norbornene 	19%	39
		mesitylene 	19%, 32%	35, 39
			28%	34
			20%	20
			36%	57
		$Cl_3C-\overset{O}{\overset{\|}{C}}-H$	59%	45
		$Cl_3C-\overset{O}{\overset{\|}{C}}-CCl_3$	54%	45
2-FC_6H_4-C≡N⁺–S⁻		$MeO_2CC\equiv CCO_2Me$	67%	14
		$HC\equiv CCO_2Et$	93%	14
4-FC_6H_4-C≡N⁺–S⁻		$MeO_2CC\equiv CCO_2Me$	49%	16

Table 2-1 The Known Nitrile Sulphides (continued)

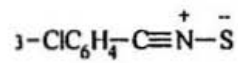
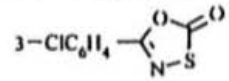
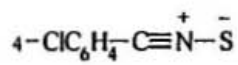
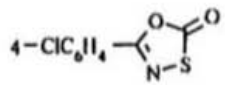
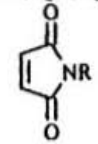
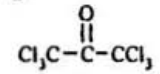
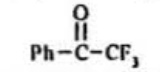
Nitrile Sulphide	Precursor	Dipolarophile	Yield of Cycloadduct(s)	Ref.
		$MeO_2CC{\equiv}CCO_2Me$	48%, 52%	14, 16
		$HC{\equiv}CCO_2Et$	95%	14
		$MeO_2CC{\equiv}CCO_2Me$	46, 58%	14, 16
		$HC{\equiv}CCO_2Et$	90%	14
		$EtO_2CC{\equiv}N$	76%	13
		$Cl_3CC{\equiv}N$	59%	41
		$PhC{\equiv}N$	36%	37
		$p\text{-}ClC_6H_4C{\equiv}N$	62%	37
		$EtO_2CCH_2C{\equiv}N$	6%	37
		$CH_2{=}CHCO_2Ph$	64%	34
		$CH_2{=}C(Cl)CO_2Et$	77%	34
		$PhCH{=}CHNO_2$	0%	34
		$3\text{-}(O_2N)C_6H_4CH{=}CH_2$	0%	34
		 (R = Et, Ph)	61%, 64%	34
			35%	45
			18%	45

Table 2-1 The Known Nitrile Sulphides (continued)

Nitrile Sulphide	Precursor	Dipolarophile	Yield of Cycloadduct(s)	Ref.
3,4-$Cl_2C_6H_3C{\equiv}\overset{+}{N}\!-\!\overset{-}{S}$		$MeO_2CC{\equiv}CCO_2Me$	71%	14
		$HC{\equiv}CCO_2Et$	88%	14
2,6-$Cl_2C_6H_3C{\equiv}\overset{+}{N}\!-\!\overset{-}{S}$		$MeO_2CC{\equiv}CCO_2Me$	30%	14
		$HC{\equiv}CCO_2Et$	86%	14
2-$CF_3C_6H_4C{\equiv}\overset{+}{N}\!-\!\overset{-}{S}$		$MeO_2CC{\equiv}CCO_2Me$	96%	14
		$HC{\equiv}CCO_2Et$	51%	14
3-$CF_3C_6H_4C{\equiv}\overset{+}{N}\!-\!\overset{-}{S}$		$(CN)_2C{=}C(CN)_2$	51% - 67%	56
		$EtO_2CC{\equiv}N$	76%	37
		$HC{\equiv}CCO_2Et$	62%	14
3,5-$(CF_3)_2C_6H_3C{\equiv}\overset{+}{N}\!-\!\overset{-}{S}$		$MeO_2CC{\equiv}CCO_2Me$	53%	14
		$HC{\equiv}CCO_2Et$	96%	14
3-$O_2NC_6H_4C{\equiv}\overset{+}{N}\!-\!\overset{-}{S}$		$MeO_2CC{\equiv}CCO_2Me$	54%	14
		$HC{\equiv}CCO_2Et$	72%	14
4-$O_2NC_6H_4C{\equiv}\overset{+}{N}\!-\!\overset{-}{S}$		$MeO_2CC{\equiv}CCO_2Me$	25%	14
		$HC{\equiv}CCO_2Et$	25%	14
4-$(NC)C_6H_4C{\equiv}\overset{+}{N}\!-\!\overset{-}{S}$		$HC{\equiv}CCO_2Et$	43%	14

Table 2-1 The Known Nitrile Sulphides (continued)

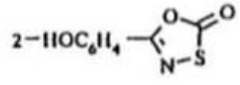
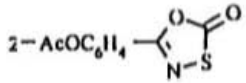
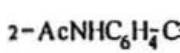
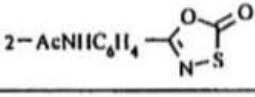
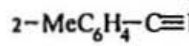
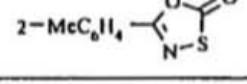
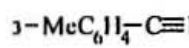
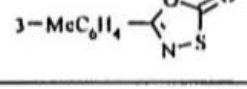
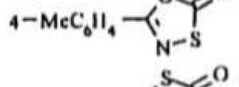
Nitrile Sulphide	Precursor	Dipolarophile	Yield of Cycloadduct(s)	Ref.
		$MeO_2CC{\equiv}CCO_2Me$	75%	12
		$HC{\equiv}CCO_2Et$	40%	12
		$EtO_2CC{\equiv}N$	85%	12
		$EtO_2CCH{=}CHCO_2Et$	15%	12
		$MeO_2CC{\equiv}CCO_2Me$	90%	12
		$HC{\equiv}CCO_2Et$	93%	12
		$EtO_2CC{\equiv}N$	73%	12
		$EtO_2CCH{=}CHCO_2Et$	56%	12
		$MeO_2CC{\equiv}CCO_2Me$	24%	12
		$EtO_2CC{\equiv}N$	98%	12
		$MeO_2CC{\equiv}CCO_2Me$	66%	14
		$HC{\equiv}CCO_2Et$	93%	14
		$MeO_2CC{\equiv}CCO_2Me$	52%	14
		$HC{\equiv}CCO_2Et$	98%	14
		$MeO_2CC{\equiv}CCO_2Me$	24% - 74%	14, 24, 55
		$EtO_2CC{\equiv}CCO_2Et$	?%	35
		$PhC(O)C{\equiv}CC(O)Ph$	?%	55

Table 2-1 The Known Nitrile Sulphides (continued)

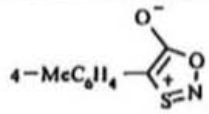
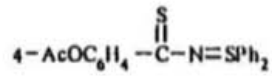
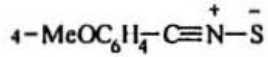
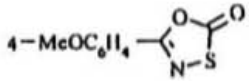
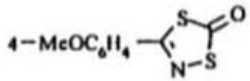
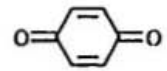
Nitrile Sulphide	Precursor	Dipolarophile	Yield of Cycloadduct(s)	Ref.
		$HC{\equiv}CCO_2Et$	90%	14
		$PhC{\equiv}N$	8%	37
		$4\text{-}MeC_6H_4C{\equiv}N$	12%	37
		$Cl_3CC{\equiv}N$	66%	41
		$4\text{-}(O_2N)C_6H_4SC{\equiv}N$	17%	58
		$2,4\text{-}(O_2N)_2C_6H_3SC{\equiv}N$	17%	58
		$2\text{-}Cl\text{-}4,6\text{-}(O_2N)_2C_6H_2SC{\equiv}N$	37%	58
		$2,4\text{-}(O_2N)_2C_6H_3SeC{\equiv}N$	18%	58
		$MeO_2CC{\equiv}CCO_2Me$	60%	16, 55
		$PhC(O)C{\equiv}CC(O)Ph$	?%	55
		$Cl_3CC{\equiv}N$	45%	41
		$4\text{-}(O_2N)C_6H_4SC{\equiv}N$	10%	58
		$1\text{-naphthyl-}SC{\equiv}N$	2%	58
		$2,4\text{-}(O_2N)_2C_6H_3SC{\equiv}N$	26%	58
		$2\text{-}Cl\text{-}4,6\text{-}(O_2N)_2C_6H_2SC{\equiv}N$	20%	58
		$PhCH{=}NPh$	2%	19
		$4\text{-}ClC_6H_4CH{=}NPh$	5%	19
		$4\text{-}(O_2N)C_6H_4CH{=}NPh$	5%	19
			34%	35

Table 2-1 The Known Nitrile Sulphides (continued)

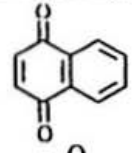
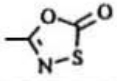
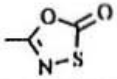
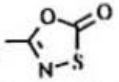
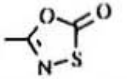
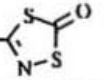
Nitrile Sulphide	Precursor	Dipolarophile	Yield of Cycloadduct(s)	Ref.
4-$MeOC_6H_4-C\equiv\overset{+}{N}-\overset{-}{S}$			42%	57
		$Cl_3C-\overset{O}{\overset{\|\|}{C}}-H$	76%	45
		$Cl_3C-\overset{O}{\overset{\|\|}{C}}-CCl_3$	57%	45
		$Ph-\overset{O}{\overset{\|\|}{C}}-CF_3$	28%	45
3,4-$(CH_2O)_2C_6H_3-C\equiv\overset{+}{N}-\overset{-}{S}$	3,4-$(CH_2O)_2C_6H_3$ 	$MeO_2CC\equiv CCO_2Me$	51%	14
		$HC\equiv CCO_2Et$	94%	14
3,4-$(MeO)_2C_6H_3-C\equiv\overset{+}{N}-\overset{-}{S}$	3,4-$(MeO)_2C_6H_3$ 	$MeO_2CC\equiv CCO_2Me$	60%, 73%	14, 16
		$HC\equiv CCO_2Et$	98%	14
3,4-$(MeO)_2C_6H_3-C\equiv\overset{+}{N}-\overset{-}{S}$	3,4-$(MeO)_2C_6H_3$ 	$HC\equiv CCO_2Et$	58%	14
		$EtO_2CC\equiv N$	94%	37
2,4,5-$Me_3C_6H_2-C\equiv\overset{+}{N}-\overset{-}{S}$	2,4,5-$Me_3C_6H_2$ 	$MeO_2CC\equiv CCO_2Me$	2.7%	30
2,3,4-$Me_3C_6H_2-C\equiv\overset{+}{N}-\overset{-}{S}$	2,3,4-$Me_3C_6H_2$ 	$MeO_2CC\equiv CCO_2Me$	29%	30

Table 2-1 The Known Nitrile Sulphides (continued)

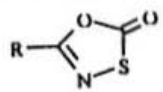
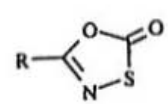
Nitrile Sulphide	Precursor	Dipolarophile	Yield of Cycloadduct(s)	Ref.
PhCH=CH–C≡N–S		$MeO_2CC{\equiv}CCO_2Me$	50%	36
		$EtO_2CC{\equiv}N$	64%	36
MeCH=CH–C≡N–S		$MeO_2CC{\equiv}CCO_2Me$	68%	36
		$EtO_2CC{\equiv}N$	64%	36
H_2C=CMe–C≡N–S		$MeO_2CC{\equiv}CCO_2Me$	34%	36
		$EtO_2CC{\equiv}N$	23%	36
H_2C=CH–C≡N–S		$MeO_2CC{\equiv}CCO_2Me$	polymerized	36
		$EtO_2CC{\equiv}N$	polymerized	36
2-$(HC{\equiv}CCO_2)C_6H_4C{\equiv}N–S$		intramolecular	20%	12
2-$(PhC{\equiv}CCO_2)C_6H_4C{\equiv}N–S$			70%	33
2-$(pClC_6H_4C{\equiv}CCO_2)C_6H_4C{\equiv}N–S$			15%	33
2-[PhC≡CC(O)NH]$C_6H_4C{\equiv}N–S$			81%	33
2-$(PhHC{=}CHCO_2)C_6H_4C{\equiv}N–S$			14%	33
2-$(pClC_6H_4CH{=}CHCO_2)C_6H_4C{\equiv}N–S$			21%	33
2-$(H_2C{=}CHCO_2)C_6H_4C{\equiv}N–S$			24%	33
2-$(EtO_2CCH{=}CHCO_2)C_6H_4C{\equiv}N–S$			28%	33

Table 2-1 The Known Nitrile Sulphides (continued)

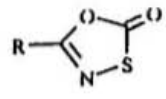
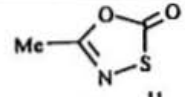
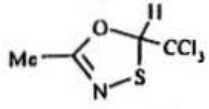
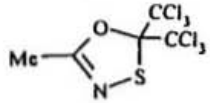
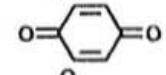
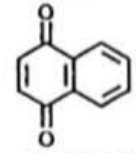
Nitrile Sulphide	Precursor	Dipolarophile	Yield of Cycloadduct(s)	Ref.
2-($pMeC_6H_4CH{=}CHCO_2$)$C_6H_4C{\equiv}\overset{+}{N}{-}\overset{-}{S}$		intramolecular	21%	33
2-($pMeOC_6H_4CH{=}CHCO_2$)$C_6H_4C{\equiv}\overset{+}{N}{-}\overset{-}{S}$			46%	33
2-(mesitylCH=CHCO$_2$)$C_6H_4C{\equiv}\overset{+}{N}{-}\overset{-}{S}$			48%	33
2-(2,6-$Cl_2C_6H_3CH{=}CHCO_2$)$C_6H_4C{\equiv}\overset{+}{N}{-}\overset{-}{S}$			59%	33
2-(PhHC=CMeCO$_2$)$C_6H_4C{\equiv}\overset{+}{N}{-}\overset{-}{S}$			5%	33
2-(PhMeC=CHCO$_2$)$C_6H_4C{\equiv}\overset{+}{N}{-}\overset{-}{S}$			15%	33
		$MeO_2CC{\equiv}CCO_2Me$	5% - 90%	14, 53, 54
		$HC{\equiv}CCO_2Et$	8%	54
		$PhC{\equiv}N$	2.7%	37
		$(NC)_2C{=}C(CN)_2$	70% - 85%	56
			19%	57
			32%	57
	$MeCH_2N{=}SF_2$	$Cl_3CC(O)H$	62%	45
		$Cl_3CC(O)CCl_3$	56%	45

Table 2-1 The Known Nitrile Sulphides (continued)

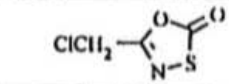
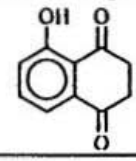
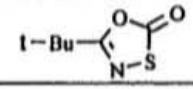
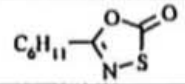
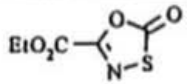
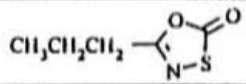
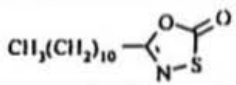
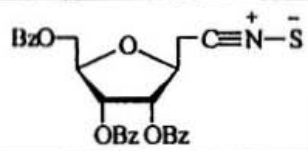
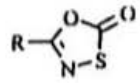
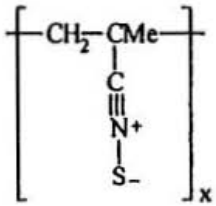
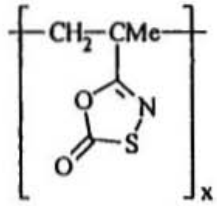
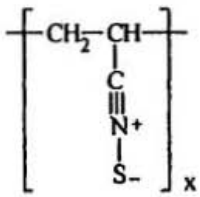
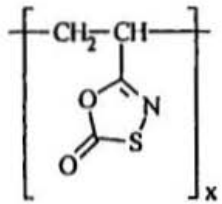
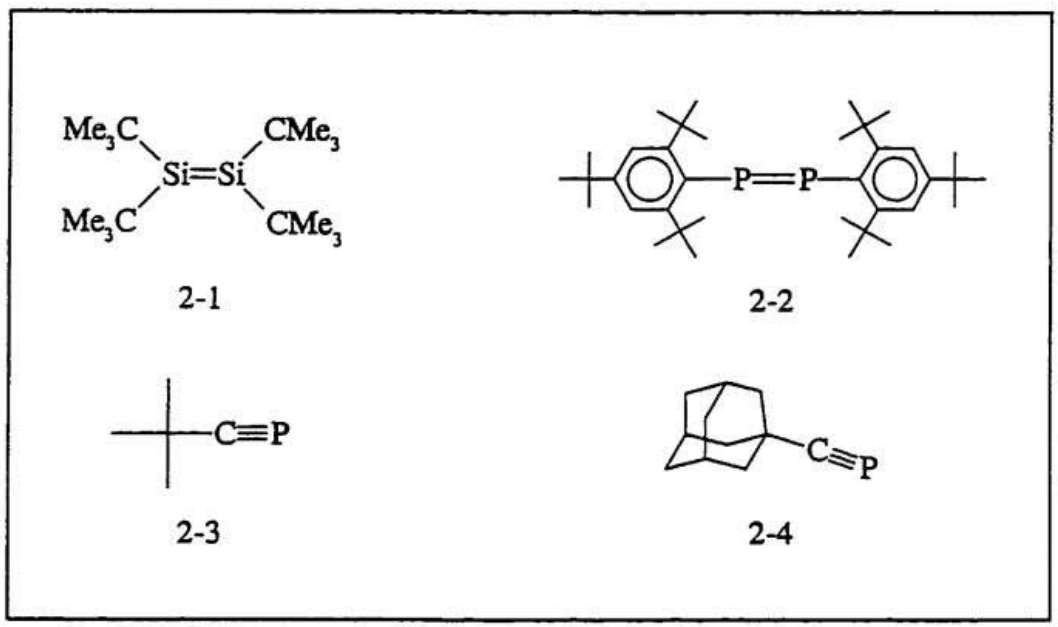
Nitrile Sulphide	Precursor	Dipolarophile	Yield of Cycloadduct(s)	Ref.
$ClCH_2-C\equiv\overset{+}{N}-\overset{-}{S}$		$MeO_2CC\equiv CCO_2Me$	32%	14
$CF_3-C\equiv\overset{+}{N}-\overset{-}{S}$	$CF_3CH_2N{=}SF_2$	$MeO_2CC\equiv CCO_2Me$	30%	54
		$HC\equiv CCO_2Me$	15%	54
			14%	54
$t\text{-}Bu-C\equiv\overset{+}{N}-\overset{-}{S}$		$MeO_2CC\equiv CCO_2Me$	24%	14
$C_6H_{11}-C\equiv\overset{+}{N}-\overset{-}{S}$		$MeO_2CC\equiv CCO_2Me$	18%	14
$EtO_2C-C\equiv\overset{+}{N}-\overset{-}{S}$		$MeO_2CC\equiv CCO_2Me$	11.7%	14
		$PhC\equiv N$	33%	13
		$p\text{-}ClC_6H_4C\equiv N$	61%	13
		$4\text{-}(EtO_2C)C_6H_4C\equiv N$	23.5%	13
		$p\text{-}MeC_6H_4C\equiv N$	7%	13
$CH_3CH_2CH_2-C\equiv\overset{+}{N}-\overset{-}{S}$		$(Cl_3C)_2C{=}O$	44%	45
$CH_3(CH_2)_{10}-C\equiv\overset{+}{N}-\overset{-}{S}$		$Cl_3CCH{=}O$	60%	45
		$(Cl_3C)_2C{=}O$	31%	45

Table 2-1 The Known Nitrile Sulphides (continued)

Nitrile Sulphide	Precursor	Dipolarophile	Yield of Cycloadduct(s)	Ref.
		$HC\equiv CCO_2Et$	64%	44
		$(EtO_2C)C\equiv N$	40%	44
		$MeO_2CC\equiv CCO_2Me$	17% - 22%	38
		$(EtO_2C)C\equiv N$	20% - 23%	38
		$MeO_2CC\equiv CCO_2Me$	10% - 17%	38
		$(EtO_2C)C\equiv N$	5% - 13%	38

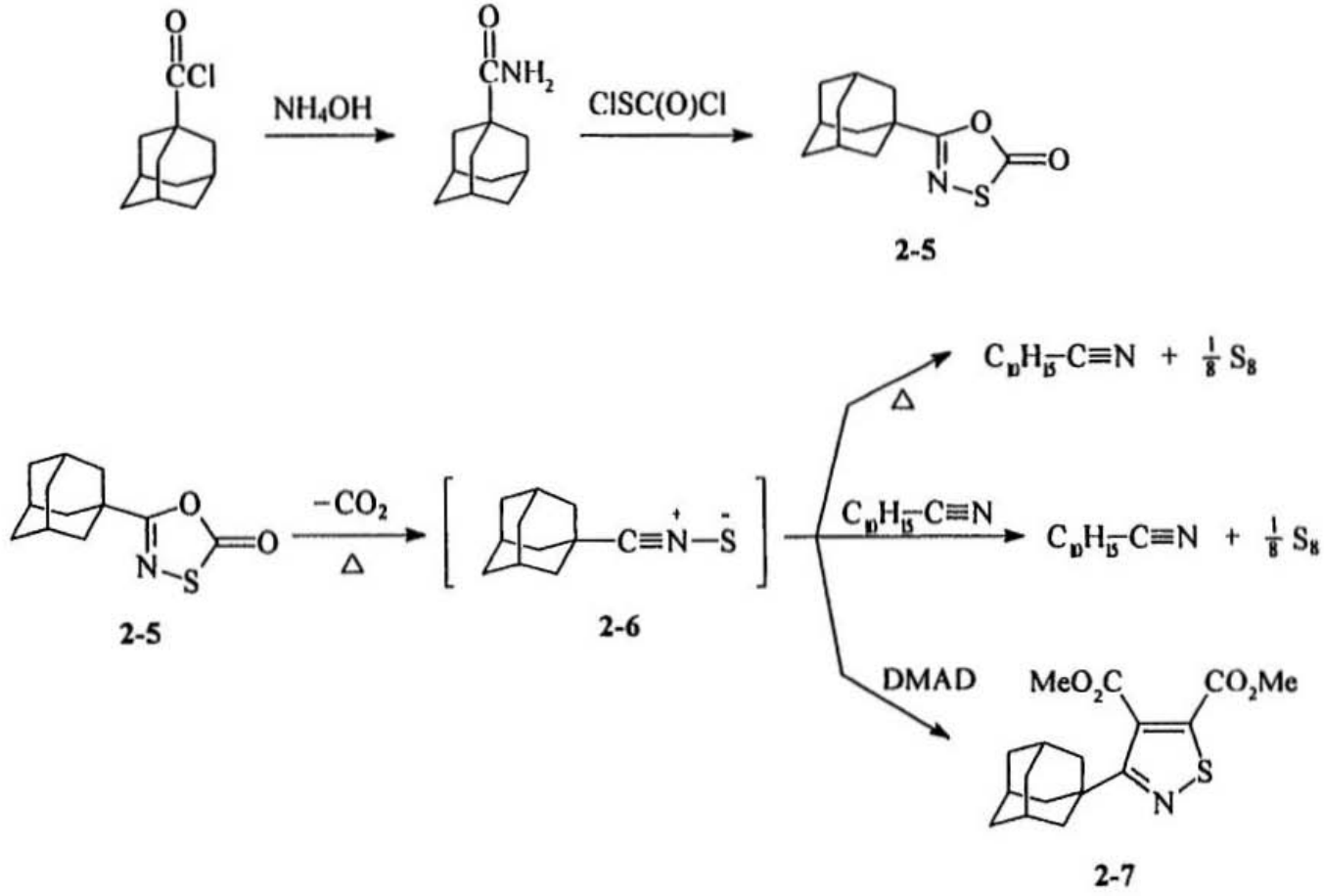
2.1.2 The Proposal

For a very long time people believed that the first row elements (C, N, O) can easily form π bonds while the heavier Main Group elements cannot (the so called *Double Bond Rule*[60]). The preparations of new compounds, for example, compounds **2-1**[61], **2-2**[62], **2-3**[63], and **2-4**[64], which contain stable π bonds to or between the heavier elements suggest that the chemistry of carbon may be a template for the discovery of new areas of Main Group chemistry. It has been realized in recent years[65,66] that all non-metals and even metals can form stable π bonds in the appropriate chemical environment and the chemistry of these kinetically stable π bonds has been described. Most of these



compounds such as **2-1** to **2-4** are actually thermodynamically unstable compared to their corresponding single bonded derivatives. They are, however, kinetically stable[61-64] under

the protection of bulky groups such as *t*-butyl (Me_3C-), adamantyl ($C_{10}H_{15}$-), mesityl (2,4,6-$Me_3C_6H_2$-), and "super mesityl" (2,4,6-$[Me_3C]_3C_6H_2$-). The same technique, "kinetic protection", has been used to isolate a 1,3-dipole, nitrile oxide, when the mesityl or "super mesityl" group was attached to it[1]. No attempt, to our knowledge, has been made to isolate a nitrile sulphide by using this technique (Table 2-1). In this Chapter, the first nitrile sulphide attached to a cage hydrocarbon, adamantyl, will be discussed along with the precursor, 5-adamantyl-1,3,4-oxathiazol-2-one, and the cycloaddition reactions of this 1,3-dipole with adamantyl nitrile, dimethylacetylene dicarboxylate (DMAD), and thiazyl chloride (Scheme 2-1).



Scheme 2-1 Generation and reactions of adamantyl nitrile sulphide

2.2 Experimental

2.2.1 General Procedures

The reagents used in synthesis; $C_{10}H_{15}C(O)Cl$, ClSC(O)Cl, and $MeO_2CC{\equiv}CCO_2Me$ (DMAD) were purchased from Aldrich and used as received. The amide $C_{10}H_{15}C(O)NH_2$ was prepared from the acid chloride and concentrated ammonia following the standard literature procedures[67]. Solvents were refluxed with the appropriate drying agent [C_6H_5Cl / P_2O_5, $C_6H_5CH_3$ / Na] and distilled under nitrogen prior to use. Air and moisture sensitive compounds were handled under a nitrogen atmosphere. Melting points were determined on a Mel-Temp II melting point apparatus and are uncorrected. Elemental analyses were carried out at Canadian Microanalytical Service Ltd., Delta, British Columbia, Canada. IR spectra were recorded from Nujol Mulls on KBr plates using a Mattson Polarish FT-IR instrument. NMR spectra were recorded on a General Electric 300 MHz instrument (^1H, ^{13}C) in $CDCl_3$ or on a Bruker AMX400 MB instrument (^{14}N) (at the Atlantic Regional Magnetic Resonance Centre). Chemical shifts are reported in ppm (high frequency positive) relative to internal standards (^1H: TMS, ^{13}C: $CDCl_3$) and external standards (^{14}N: CH_3NO_2). Mass spectra were recorded on a VG Micromass 7070HS double focusing spectrometer. UV-visible spectra were recorded on a Varian Cary 5E UV-Vis-NIR spectrophotometer.

2.2.2 Preparation of 5-Adamantyl-1,3,4-Oxathiazol-2-one

Chlorocarbonylsulfenyl chloride, ClSC(O)Cl, (23.2 g, 177 mmol) was added to a

mixture of toluene (125 mL) and adamantyl carbonamide, $C_{10}H_{15}C(O)NH_2$, (15.9 g, 88.6 mmol) under nitrogen to give a clear yellow solution over a white solid. The solution was heated at 90-100 °C and maintained at that temperature range for three hours. The resulting clear yellow-brown solution was poured into a crystallizing dish and allowed to evaporate to dryness to give a dark brown crystalline solid (19.4 g) which was transferred to a sublimation apparatus and heated at 30-55 °C [10^{-3} mmHg] for 20 hr to give a white sublimed solid (17.9 g) and a non-sublimed brown residue. The white solid was recrystallised from hexanes to give clear colorless plate shaped crystals of 5-adamantyl-1,3,4-oxathiazol-2-one **2-5** (17.4 g, 83%), m.p. 68-70 °C, UV-vis [λ_{max}(hexane)/nm (ε/dm^{3}mol^{-1}cm^{-1})]: 214 (7,900); IR (cm^{-1}): 1815 (sh), 1766 (s), 1730 (ms), 1594 (ms), 1377 (m), 1101(w), 997 (ms), 907(ms). NMR, ^{1}H δ: 2.09-1.76 (m, 15H); ^{13}C δ: 174.8 (C=O), 167.3 (C_{het}), 38.9 (CH_2), 38.5 (C_{quat}), 36.1 (CH_2), 27.5 (CH); ^{14}N δ ($\Delta\nu^{1/2}$ Hz): -160 (950). MS [IE, 70eV] *m/e* (%): 237 (12, M^+), 193 (1, $C_{10}H_{15}$-CNS), 161 (12, $C_{10}H_{15}$-CN), 135 (100, $C_{10}H_{15}$). Anal. calcd.: C 60.73, H 6.37, N 5.90; found: C 59.27, H 6.27, N 5.71.

2.2.3 Reaction of 5-Adamantyl-1,3,4-Oxathiazol-2-one with DMAD

5-Adamantyl-1,3,4-oxathiazol-2-one **2-5** (2.4 g, 10 mmol) was dissolved in chlorobenzene (~25 mL) and added dropwise to a refluxing mixture of chlorobenzene (~25 mL) and MeO_2CCCCO_2Me, DMAD (1.5 g 11 mmol). The addition was completed in 5 hr under nitrogen. The reaction mixture was refluxed for 20 hr to give a light brown solution from which an oily yellow brown solid (2.6 g) was recovered by solvent

evaporation and exhaustive evacuation. The solid was dissolved in $CHCl_3$ and passed through a column (silica gel 240-400 mesh) to give a light-yellow solid (1.9 g) which was transferred to a sublimation apparatus and heated at 50 °C [10^{-3} mmHg] for several days. The yellow-white solid (0.94 g) which sublimed to the cold finger was shown to be a mixture of the product dimethyl 3-adamantyl-isothiazole-4,5-dicarboxylate **2-7** and $C_{10}H_{15}$-CN by NMR and mass spectroscopy. The non-sublimed yellow-white solid was shown to be pure isothiazole **2-7** (0.90 g, 2.68 mmol, 26.8%). The product was recrystallised from $CHCl_3$ to give clear colorless plate shaped crystals of compound **2-7**, m.p. 117.5-118.5 °C, UV-vis [λ_{max}(hexane)/nm (ε/dm^{3}mol^{-1}cm^{-1})]: 278.7 (4,700), 231.1 (5,200), 192.2 (11,000); IR (cm^{-1}): 1739 (s), 1531 (m), 1366 (w), 1271 (ms), 1245(ms), 1133 (m), 1016(m), 983 (w), 801(w), 777 (w). NMR, ^{1}H δ: 3.97/3.90 (s, 6H), 2.06 (m, 9H), 1.75 (m, 6H); ^{13}C δ: 175.5 (C=O), 166.3 (C=O), 159.5 (C_{het}), 154.6 (C_{het}), 132.8 (C_{het}), 53.0/52.8 (OMe), 40.8 (CH_2), 40.4 (C_{quat}), 36.4 (CH), 28.4 (CH_2); ^{14}N δ ($\Delta\nu^{1/2}$ Hz): -87 (2500). MS [IE. 70eV] *m/e* (%): 335 (84, M$^+$), 320 (100), 304 (27), 303 (27), 276 (16), 275 (24), 245 (22), 79 (21), 41 (25). Anal. calcd.: C 60.88, H 6.31, N 4.18; found: C 60.43, H 6.28, N 4.18.

2.2.4 Reaction of 5-Adamantyl-1,3,4-Oxathiazol-2-one and Adamantyl Nitrile

A sample of the solution of 5-adamantyl-1,3,4-oxathiazol-2-one **2-5** (0.24 g, 1.0 mmol) and $C_{10}H_{15}$-CN (0.16 g, 1.0 mmol) in 3 mL of chlorobenzene was placed in a NMR tube. The ^{13}C NMR spectral data were collected every 42 min. at 125°C for 5 hr. The spectra showed the disappearance of one set of adamantyl peaks. The remaining

sample from the same solution was heated to reflux for 8 hr. to give a clear yellow solution from which a yellow solid was recovered by solvent evaporation. The ^{13}C NMR spectrum of the resulting solid in $CDCl_3$ showed the peaks [125.1 (C≡N), 39.7, 35.6, 27.0 ppm] (**Appendix 1**).

2.3 Results and Discussion

2.3.1 Preparation of 5-Adamantyl-1,3,4-oxathiazol-2-one

As indicated in Table 2-1, nitrile sulphides are mostly generated from the precursors 1,3,4-oxathiazol-2-ones. Most of the known oxathiazolones are directly connected to aromatic rings. The eight known alkyl derivatives of the oxathiazolone heterocycle have been prepared by the reaction of the amide with chlorocarbonylsulfenyl chloride. In fact no adamantyl derivatives have been reported. The preparation of 5-adamantyl-1,3,4-oxathiazol-2-one **2-5** from adamantyl carbonamide and chlorocarbonylsulfenyl chloride in hot toluene produced a mixture of products: the desired oxathiazolone, sulphur and adamantyl nitrile (HCl and CO_2 were given off as gases). The latter two products (HCl and CO_2) are undoubtedly produced from the decomposition of the oxathiazolone following the elimination of CO_2 as shown in Scheme 2-1. Unfortunately, when the reaction was run for longer periods at lower temperature to limit this decomposition, the oxathiazolone was obtained in lower yield and was mixed with the starting amide. Therefore, the preparation was typically conducted at 90-100 °C in

toluene and the product had to be purified by sublimation (to remove tarry impurities) and then recrystallised several times from hexanes to give a pure crystalline product (clear colorless). The pure crystalline solid was observed to acquire a distinct light violet color when exposed to daylight on the bench and to lose the color when redissolved in any solvent. When the light violet crystals were dissolved in hexane or chloroform, a light pinkish solution was obtained and the color could stay in the solution for several hr. The change in color did not lead to any changes in the observed physical (m.p.) or spectroscopic (UV-vis, NMR, and IR) properties. The ^{13}C NMR of derivatives of this heterocyclic family have two characteristic resonances at 174.2 ± 0.6 ppm [C=O] and 162 ± 5.3 ppm [C=N] based on previously published spectra which correspond to resonances observed in the ^{13}C NMR spectrum of **2-5** (174.8 and 167.3 ppm). The mass spectrum of **2-5** showed a peak (*m/e* 193) assigned to the nitrile sulphide or its equivalent fragment at very low intensity (1%) which may be evidence of the existence of the nitrile sulphide (see section 1.2).

2.3.2 Generation and Attempted Isolation of Adamantyl Nitrile Sulphide

The generation of the nitrile sulphides *in situ* from oxathiazolones and other precursors has been well studied[7,59] while a stable nitrile sulphide has never been isolated. As mentioned before, the nitrile sulphide will quickly decompose to a nitrile and elemental sulphur in the absence of a dipolarophile. In order to isolate the thermodynamically unstable species, protective bulky groups are often used so that the kinetically stabilized compounds can be isolated. Mesityl and "super mesityl" have been

used for the isolation of the nitrile oxide[1]. Other sterically bulky groups[61,63,64,68,69] (see 2.1.1) have been widely used to isolate thermodynamically unstable species such as phosphaalkene[70] (-P=C<), phosphaalkyne[65,70] (-C≡P), disilene[61] (>Si=Si<), diphosphene[62,70,71] (-P=P-), and diarsenene[69] (-As=As-). In this work, the adamantyl group was chosen for the attempted isolation of a nitrile sulphide. The decomposition of 5-adamantyl-1,3,4-oxathiazol-2-one **2-5** in hot toluene quantitatively gave only adamantyl nitrile and elemental sulphur in the absence of a dipolarophile. The mesitylnitrile oxide ($2,4,6\text{-}Me_3C_6H_2\text{-}C{\equiv}N\text{-}O$) was observed to dimerize or to polymerize under the same conditions[1]. Even the mass spectrum of 5-adamantyl-1,3,4-oxathiazol-2-one gave only a 1% intensity peak of adamantyl nitrile sulphide or its equivalent fragment, indicating that the adamantyl group does not stabilize the nitrile sulphide or at least not in the thermal decomposition of the oxathiazolone. Neil Squires[72], working in this group, has attempted to isolate nitrile sulphide derivatives attached to other bulky groups (mesityl and "super mesityl") by using the same methodology. He had difficulties, however, to get the pure precursors 5-(2',4',6'-trimethylphenyl)-1,3,4-oxathiazol-2-one and 5-(2',4',6'-tri-*tert*-butylphenyl)-1,3,4-oxathiazol-2-one.

Although attempts to isolate a nitrile sulphide by using sterically bulky groups were not successful, it may still be possible to prepare a stable nitrile sulphide if a method which does not involve thermochemical or photochemical processes is found. The stable 2,4,6-trimethylbenzonitrile oxide[73] was generated from the dehydrogenation of 2,4,6-trimethylbenzaldoxime (Ar-CH=NOH) with sodium hypobromite, NaOBr, at 0-5 °C.

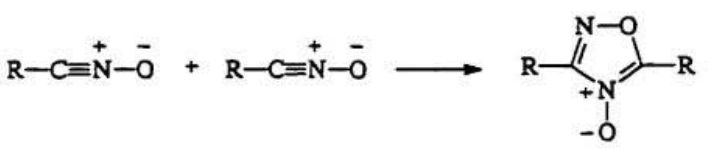
This may suggest that low temperature reactions in addition to the use of sterically bulky groups should be taken into account when the precursors or new methods are designed for the generation of a kinetically stable nitrile sulphide.

2.3.3 Cycloaddition Reactions of Adamantyl Nitrile Sulphide with Dipolarophiles

Due to their thermal instabilities, the cycloaddition reactions of nitrile sulphides with dipolarophiles always give a mixture of cycloadduct(s), decomposition products (R-C≡N and S_8) and sometimes other minor by-product(s) (for example, tetramethyl tetracarboxylatethiophene in the case of DMAD as the dipolarophile). The yields of the products are determined by the competition between the decomposition and the cycloaddition reactions. The cycloaddition reaction of adamantyl nitrile sulphide with DMAD (C_6H_5Cl, 135 °C, 0.2 M) gave the cycloadduct dimethyl 3-adamantylisothiazole-4,5-dicarboxylate **2-7** (27%), adamantyl nitrile, and sulphur. The separation of adamantyl nitrile from the cycloadduct is a problem. Sublimation and column chromatography using a variety of solvent combinations did not give adequate separation of the two species. The same difficulty was confronted in the separation of adamantyl nitrile from the oxathiazolone **2-5**. Valerie Jefford[74], working in this group, found that tungsten hexacarbonyl can selectively coordinate to adamantyl nitrile to form tungsten adamantyl nitrile pentacarbonyl complex. This reaction provided a way to purify the oxathiazolone **2-5** and the isothiazole **2-7**.

The saturated nitrile sulphides are relatively inactive towards dipolarophiles compared to the aromatic nitrile sulphides. This is due to the conjugation between the

aromatic ring and the dipole which reduces the HOMO-LUMO gap of the aromatic nitrile sulphides and therefore increases the reactivity of the dipoles. This may also mean that saturated nitrile sulphides will usually decompose much more than they will undergo cycloaddition reactions. The yields from the known saturated nitrile sulphides (CH_3, $ClCH_2$, *t*-Butyl, and cyclohexyl) with DMAD (one of the best dipolarophiles) are between 18%-50%[14]. Adamantyl nitrile sulphide shows a similar reactivity to DMAD. Although nitriles are surprisingly reactive towards aromatic nitrile sulphides[7], they are not very reactive towards saturated nitrile sulphides (Table 2-1). Only methyl nitrile sulphide reacted with benzonitrile at 193 °C to give 2.7% of the cycloadduct. In this work it has been shown that adamantyl nitrile sulphide did not react with adamantyl nitrile. The cycloadduct (including the possible dimerized nitrile sulphides **2-9**, see Scheme 2-2) could not be detected in the chlorobenzene solution of the oxathiazolone **2-5** and adamantyl



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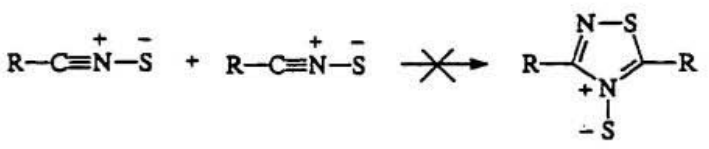


2-9

Scheme 2-2

nitrile even after refluxing overnight. The results suggest that under these conditions the decomposition of adamantyl nitrile sulphide is much faster than its cycloaddition to a dipolarophile.

2.3.4 Structure of Dimethyl 3-Adamantylisothiazole-4,5-Dicarboxylate

The ^{1}H and ^{13}C NMR spectra of the DMAD cycloadducts of nitrile sulphides have been compiled[75] and generally show two resonances in the range 155 ± 11 ppm (this work: 159.5 and 154.6 ppm) and a third resonance in the range 128 ± 18 ppm (this work: 132.0 ppm) for the three endocyclic carbon atoms. The spectra of **2-7** were also consistent with a DMAD molecule incorporated into the five-membered ring (IR: strong carbonyl band at 1739 cm^{-1}, ^{1}H NMR: two OCH_3 resonances at 3.97 and 3.90 ppm, ^{13}C NMR: two OCH_3 resonances at 53.1 and 52.9 ppm and two C=O resonances at 175.5 and 166.3 ppm). The identity of the product was also supported by the mass spectrum which gave the expected molecular ion and the fragments generated by loss of Me, OMe, and CO_2Me in sequence.

The structures of isothiazole heterocycles have been studied by microwave spectroscopy[76,77] but few crystal structures of isothiazoles have been reported[75,78,79] before. The crystal structure of compound **2-7** was the first structure of an isothiazole that was a cycloadduct of DMAD and a nitrile sulphide. Clear colorless plate-shaped crystals of compound **2-7** were grown by slowly diffusing hexanes into the chloroform solution of the compound. The crystallographic data were collected at room temperature (26 ± 1°C) on a Rigaku AFC6S diffractometer and a 2KW sealed tube generator and the structure

was solved by Dr. John N. Bridson at this department (so were those for the rest of novel compounds in this work unless specified). Most[80] of the data and important bond distances and angles for compound **2-7** are given in **Appendix 2**. The structure was consistent with those reported for the molecules containing DMAD, isothiazole or adamantyl moieties. The carbon-sulphur bond (C_3-S_1: 1.690(4) Å, reported average[75]: 1.720 Å) and the carbon-carbon bond (C_1-C_2: 1.429(6) Å, reported average[75]: 1.454 Å), however, are significantly shorter than the related bonds in the previously reported isothiazole structures. These structural variations may be due to the influence of π bond delocalization to the methyl carboxylate moieties. The structure of **2-7** collected and solved normally, but a second partial image of the skeleton rotated by 60° appeared in the difference maps. Attempts to locate all the atoms were unsuccessful, but the three atoms bonded to the pivotal carbon atom showed up clearly in both major and minor[80] images (which exist in a ratio of 7:3) permitting placement of the missing atoms in calculated positions. Diagrams and data are given for the major orientation of the adamantyl group. The minor orientation of the adamantyl group could probably be another comparably thermodynamically stable conformation of the molecule caused by the attempted rotation of the other methyl carboxylate group to conjugate with the heterocyclic π system.

2.3.5 Conclusions and Future Work

The precursor 5-adamantyl-1,3,4-oxathiazol-2-one **2-5** was synthesized. It gave, upon heating, the unstable intermediate adamantyl nitrile sulphide **2-6** which could be

trapped by DMAD (a dipolarophile) to form the cycloadduct, dimethyl 3-adamantylisothiazole-4,5-dicarboxylate **2-7** in 27% yield but did not react with adamantyl nitrile under our conditions. The unsuccessful attempts to isolate the 1,3-dipole **2-6** does not necessarily mean that the bulky group adamantyl could not stabilize the intermediate **2-6**. It may imply that a better designed reaction is required. It will be worth of trying a low temperature reaction to generate as well as to isolate a nitrile sulphide.

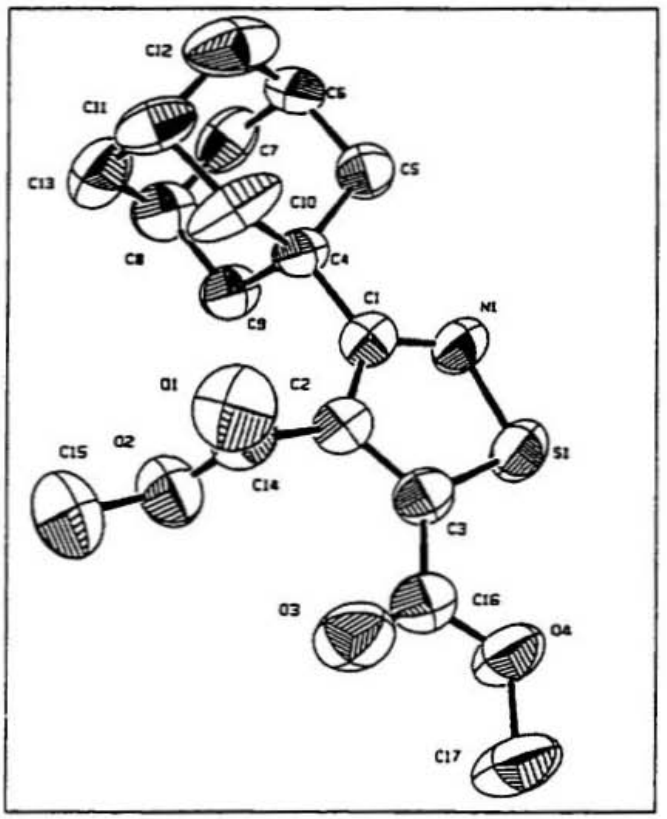


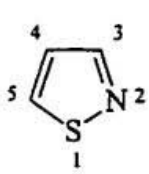
Figure 2-3 ORTEP view of dimethyl 3-adamantylisothiazole-4,5-dicarboxylate **2-7**

3.1 Introduction

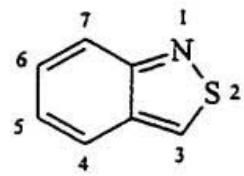
Bicyclic and polycyclic fused ring systems[85,86] (**3-2** to **3-6**) containing the 1,2-thiazole heterocyclic ring have been known for more than a century. Monocyclic isothiazoles[81-84] (**3-1**), however, were first reported in 1956. Several synthetic routes[82] to this family of heterocycles were reported before it was discovered that the reactions of nitrile sulphides (**1-2**) with alkynes gave isothiazoles in good yield[8]. The reactions of nitrile sulphides with alkynes is limited to highly activated alkynes but still provides a convenient, high yield synthesis of 3-substituted isothiazoles[87]. Common alkynes of this type that have been used in the 1,3-dipolar cycloaddition reactions are DMAD and ethyl propiolate. Since the carbonyl group can be easily converted into other organic functional groups, it is still possible and also practical to synthesize the isothiazoles substituted at positions 4 and 5 after forming the isothiazole rings by the reactions of nitrile sulphides with the limited selection of alkynes.

The monocyclic isothiazole structure has been found in many natural products and synthetic molecules which have been shown to have biological activity[82,83,88-90]. Most of them have only one isothiazole unit. Franz and Howe found that 3-aryl-isothiazole-4-carboxylic acids can be effective plant growth regulants[88] as well as effective herbicides[89]. It has been shown that two isothiazole units bridged by sulphur can be effective fungicides[83] as well.

In recent years poly(heterocycles) [In this thesis, poly(heterocycles) are systems where the heterocyclic moieties are connected to each other but not fused. Compounds



3-1



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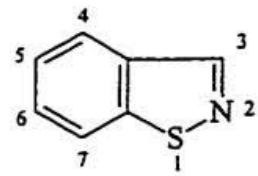

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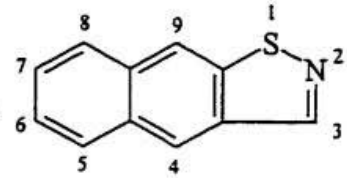

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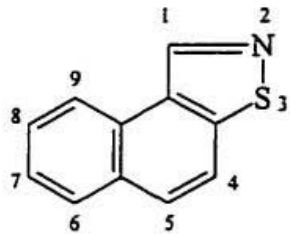
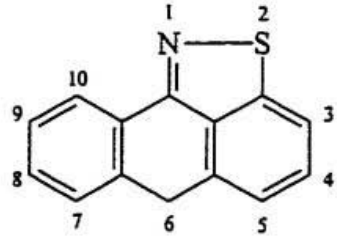


3-5



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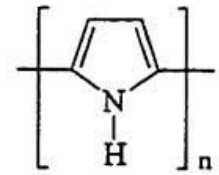

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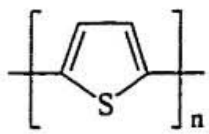

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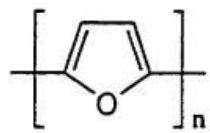

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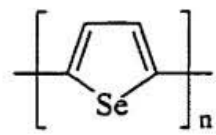

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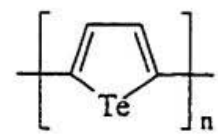

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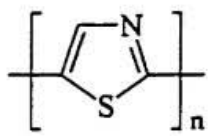

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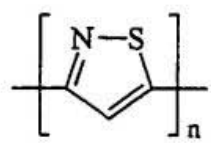

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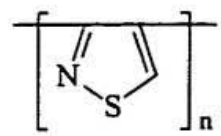

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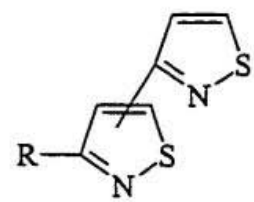
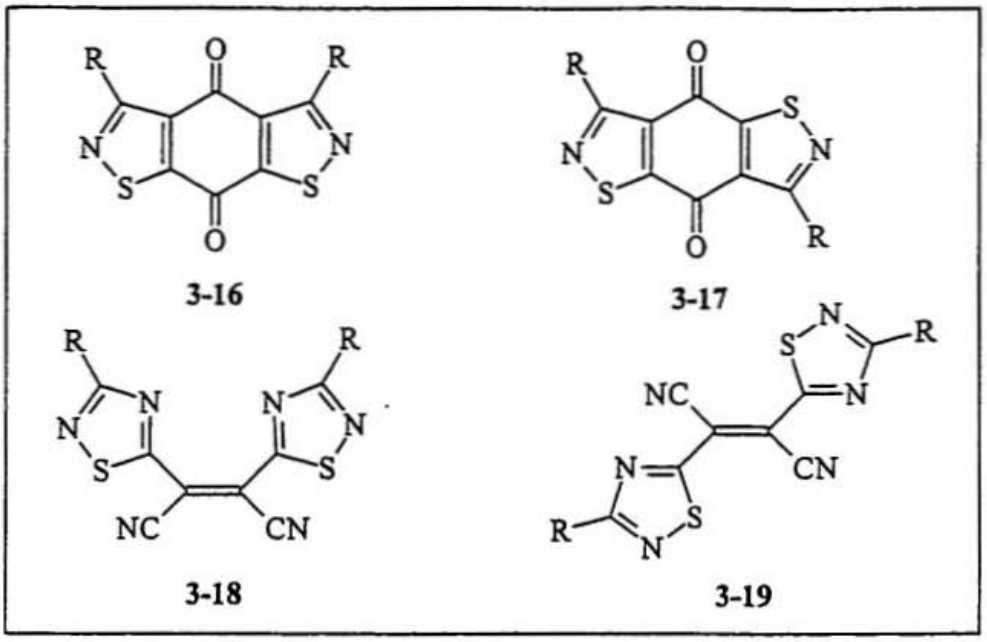
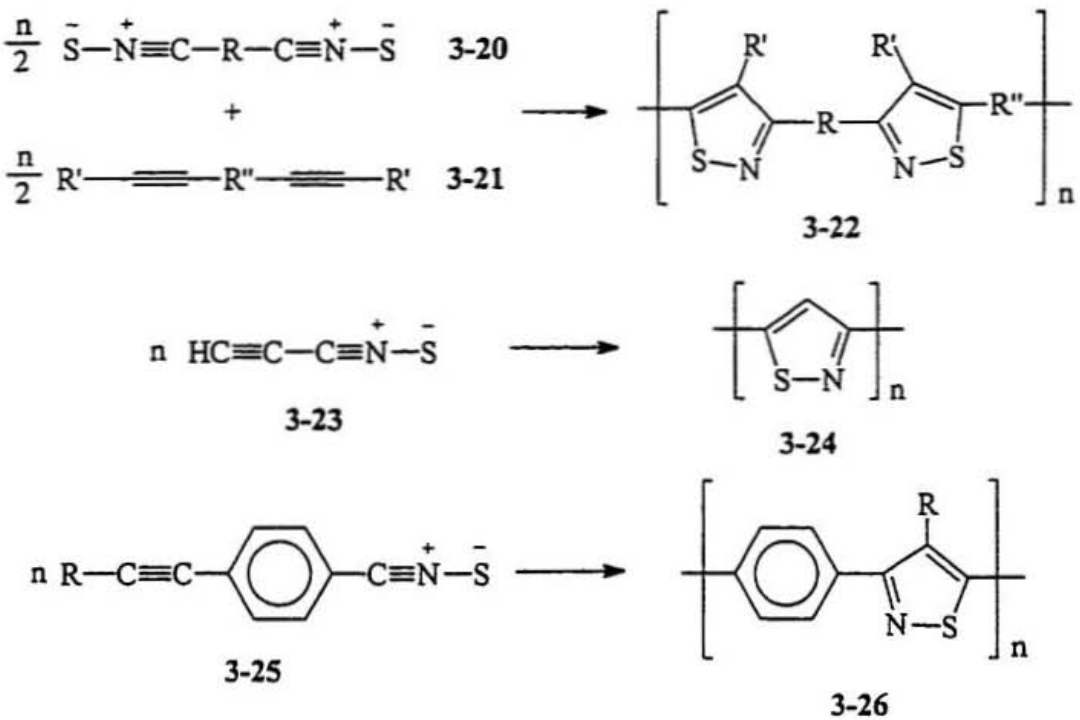


3-15

3-7 to 3-15 are examples of these systems.] have been attracting increasing interest from both academic and industrial researchers for their potential utility as new materials[91-97]. Many of these poly(heterocyclic) systems have been synthesized and their applications as new materials have been studied, for example, poly(pyrrole)[91] (3-7), poly(thiophene)[91,93,96] (3-8), poly(furan)[91] (3-9), poly(selenophene)[91] (3-10), poly(tellurophene)[91] (3-11), and poly(thiazole)[91,95,97] (3-12). The high environmental stability (e.g. physically and chemically stable towards the environment where they are in use) and the structural versatility of these electron rich conjugated poly(arylene) systems have led to their development in many applications such as conductors, electrode materials, and organic semiconductors[96]. Although isothiazoles have been incorporated into a wide range of polymeric compounds[38], there has been no report either on poly(isothiazoles) (3-13, 3-14) or on any attempt to prepare the extended isothiazole ring systems (3-15). There have been, however, some reports on compounds containing two isothiazole units [(3-16)[57], (3-17)[57], (3-18)[55], and (3-19)[55]].

Since 1,3-dipolar cycloaddition reactions of nitrile sulphides with electron deficient alkynes provide an alternative approach to isothiazoles, it may be possible to use this methodology to build up poly(isothiazoles) either by the reaction of multiple -C≡N$^+$-S$^-$ units with multiple -C≡C- units or by building up isothiazole rings one by one via the reaction of the isothiazole nitrile sulphide with alkynes (scheme 3-1). The starting materials for isothiazoles prepared by one of these routes are the oxathiazolones, the precursors of nitrile sulphides, and alkynes. In order to prepare conjugated

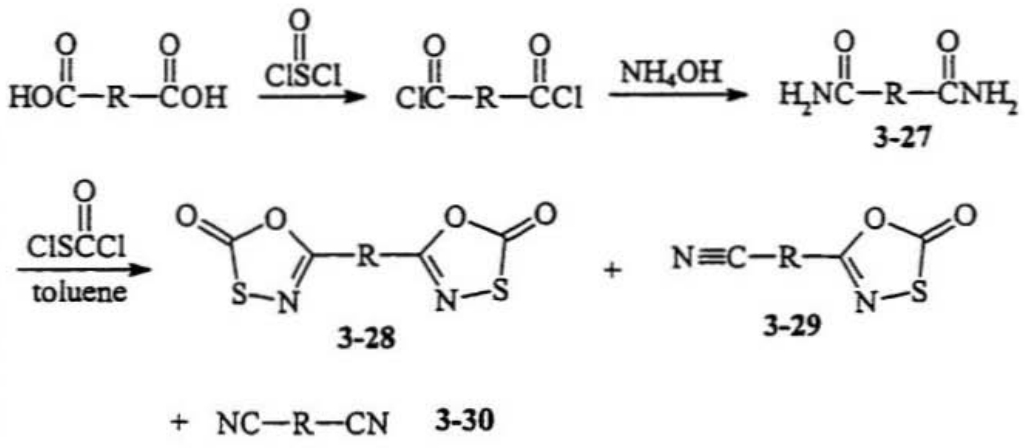




Scheme 3-1. Some proposed nitrile sulphides and alkynes

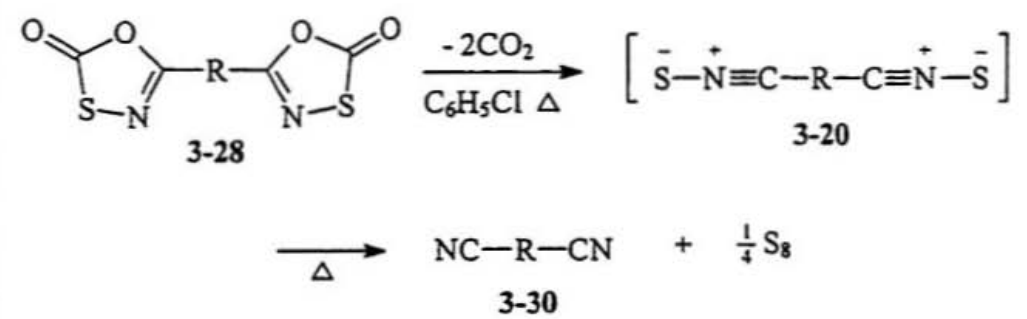
poly(isothiazoles), it will be critical to carefully design the starting materials and/or the synthetic route. Our first idea would be to generate nitrile sulphides with multiple -C≡N^{+}-S^{-} units which can react with a molecule containing more than one C≡C bond although it does not necessarily mean that the reaction of a multiple C≡N^{+}-S^{-} unit with a multiple C≡C bond will definitely give a poly(isothiazoles). The idea is to examine the reaction itself which, we hope, could provide the information to eventually help us to synthesize the poly(isothiazole) systems. The simplest nitrile sulphide of this type would be one having two C≡N-S units as in compound **3-20** whereas the simplest alkynes would have two C≡C bonds such as compound **3-21** (Scheme 3-1). The intermolecular cycloaddition reactions of compound **3-23** or **3-25** (Scheme 3-1), if available, could also be used to prepare compounds **3-24** and **3-26**.

In the 26-year history of the chemistry of nitrile sulphides there has been no report on the application of nitrile sulphides to poly(isothiazoles) by using their 1,3-dipolar cycloaddition reactions nor on the generation of a poly(nitrile sulphide). In this Chapter, the first bis(nitrile sulphides) or their synthetic equivalents, the precursor bis(oxathiazolones) and the cycloaddition reactions of bis(nitrile sulphides) with different alkynes (Scheme 3-2) will be described. The generation of the aryl and isothiazole based nitrile sulphides will also be presented (Scheme 3-3). The possibility of making poly(isothiazoles) *via* the bis(nitrile sulphides) and alkynes (two isothiazole rings are built up in the same reaction) or *via* the isothiazole nitrile sulphides and alkynes (one isothiazole ring is built up by another) will be discussed.



a. R = $C_{10}H_{14}$; b. R = $(CH_2)_8$; c. R = CH_2; d. R = 1,4-C_6H_4.

Scheme 3-2. Preparation of bis(oxathiazolones) 3-28



a. R = $C_{10}H_{14}$; b. R = $(CH_2)_8$; c. R = CH_2; d. R = 1,4-C_6H_4.

Scheme 3-3. Decomposition of bis(oxathiazolones) 3-28

3.2 Experimental

3.2.1 General Procedures

Reagents used in synthesis; 1,3-$C_{10}H_{14}[C(O)OH]_2$, 1,4-$C_6H_4[C(O)OH]$, $H_2NC(O)CH_2C(O)NH_2$, $H_2NC(O)(CH_2)_8C(O)NH_2$, $ClSC(O)Cl$, $MeO_2CC{\equiv}CCO_2Me$ (DMAD), $PhC(O)NH_2$ and $HCC{\equiv}CCO_2Et$ were purchased from Aldrich and used as received. Solvents were refluxed with the appropriate drying agent [C_6H_5Cl / P_2O_5, 1,2-$Cl_2C_6H_4$ / CaH_2, $C_6H_5CH_3$ / Na] and distilled under nitrogen prior to use. Spectral measurement was described in Chapter 2.2.1 unless specified (so were treated in Chapters 4.2. and 5.2.).

3.2.2 Preparation of 1,3-Adamantanedicarbonamide, 3-27a

A mixture of thionyl chloride (~70 mL) and 1,3-adamantanedicarboxylic acid (5.6 g, 25 mmol) was refluxed until it turned to a clear solution. The excess thionyl chloride was removed by regular distillation and the product 1,3-adamantanedicarboxylic chloride (6.4 g), a white solid, was dried at room temperature under vacuum (10^{-3} mmHg). Ammonium hydroxide (30%, 120 mL) was added to the crude product and the mixture was heated to reflux with stirring for three hours. White solids were filtered and washed several time with water. The pure, colorless cube shaped crystals of 1,3-adamantanedicarbonamide **3-27a** (5.1 g, 94%) were recrystallized from H_2O:EtOH (10:1). The amide **3-27a** is insoluble in most organic solvents, slightly soluble in H_2O, and soluble in dimethylsulfoxide (DMSO), m.p. 254-256°C (literature[99]: m.p.255°C); IR(cm^{-1}):

3399 (s), 3350 (s), 3273 (s), 3211 (s), 1693 (s), 1644(s), 1608 (s). NMR [$CD_3S(O)CD_3$], ^1H δ: 6.99 (s, 2H), 6.74 (s, 2H), 2.04-1.58 (m, 14H); ^{13}C δ: 178.9 (C=O), 40.2 (CH_2), 38.9 (CH_2), 38.0 ($2CH_2$), 27.9 ($2CH_2$).

3.2.3 Preparation of 1,3-bis(1',3',4'-Oxathiazol-2'-one-5'-yl)-adamantane, 3-28a, 1-cyano-3-(1',3',4'-oxathiazol-2'-one-5'-yl)-adamantane, 3-29a, and 1,3-adamantanedinitrile, 3-30a

Chlorocarbonylsulfenyl chloride, ClSC(O)Cl, (9.4 g, 72 mmol) was added to a mixture of toluene (70 mL) and 1,3-adamantanedicarbonamide, $C_{10}H_{14}[C(O)NH_2]_2$, (4.0 g, 18 mmol), under nitrogen to give a clear yellow solution over a white solid. The solution was heated at 90-100 °C and maintained at that temperature range for 11 hours. The resulting clear orange solution was subjected to rotary evaporation (60°C water bath) to remove the excess ClSC(O)Cl and solvent, and a wet yellow solid (6.8 g) was obtained. The mixture was dissolved in $CHCl_3$ and passed through a column (silica gel, 240-400 mesh) to give a white solid 1,3-bis(1',3',4'-oxathiazol-2'-one-5'-yl)-adamantane (**3-28a**) (2.9 g, 8.6 mmol, 48%). This solid was recrystallised from a 5:1 EtOH:$CHCl_3$ solvent mixture to give clear colorless needle shaped crystals, m.p. 134-140°C (dec.), UV-vis [λ_{max}(hexane)/nm (ε/$dm^3mol^{-1}cm^{-1}$)]: 214 (18,000); IR (cm^{-1}): 1959 (w), 1934 (w), 1896 (w), 1873 (w), 1815 (m), 1803 (m), 1769 (ms), 1743 (ms), 1596 (ms), 1262 (ms), 1222 (ms), 1085(m), 973 (ms), 921(ms). NMR (in $CDCl_3$), ^1H δ: 2.31(m, 2H), 2.22(s, 2H), 2.07(m, 2H), 2.04(m, 2H), 1.98(m, 2H), 1.94(m, 2H), 1.78(m, 2H); ^{13}C δ: 174.0 (C=O), 165.5 (C_{het}), 39.7 (C_{quat}), 38.5 (CH_2), 37.8 (CH_2), 34.6 (CH_2), 27.2 (CH); MS [IE, 70eV] *m/z* (%): 338 (16, M^+), 294 (0.3, [NS(O)COC]$C_{10}H_{14}$-CNS), 262 (2,

[NS(O)COC]$C_{10}H_{14}$-CN), 236 (100, $C_{10}H_{14}$[COC(O)SN]), 160 (30, $C_{10}H_{14}$-CN). Anal. calcd.: C 49.7, H 4.2, N 8.3, S 19.0%; found: C 49.8, H 4.2, N 8.2, S 19.1%.

From the original column a second white solid 1-cyano-3-(1',3',4'-oxathiazol-2'-one-5'-yl)adamantane [CN-$C_{10}H_{14}$[COC(O)SN] (**3-29a**) (1.1 g, 4.2 mmol, 23%) was recovered and recrystallized from acetone to give clear colorless plate shaped crystals, m.p. 104-120°C (dec.); UV-vis [λ_{max}(hexane)/nm (ε/dm^{3}mol^{-1}cm^{-1})]: 214 (9,000); IR (cm^{-1}): 2230 (w), 1958 (w), 1895 (w), 1841 (w), 1802 (m), 1764 (ms), 1740 (ms), 1588 (m), 1247 (m), 1109 (m), 1033 (w), 976 (ms), 920(ms). NMR, ^{1}H δ: 2.20(m, 4H), 2.04-1.85(m, 8H), 1.69(m, 2H); ^{13}C δ: 173.7 (C=O), 164.7 (C_{het}), 123.5 (C≡N), 40.3 (C_{quat}), 38.5 (C_{quat}), 37.7 (CH_2), 37.3 (CH_2), 34.1 (CH_2), 30.1 (CH), 26.5 (CH_2); MS [IE, 70eV] *m/z* (%): 262 (7, M$^+$), 186 (32, $C_{10}H_{14}$[CN]$_2$, 160 (100, $C_{10}H_{14}$-CN). Anal. calcd.: C 59.5, H 5.4, N 10.7%; found: C 58.5, H 5.3, N 10.6%.

The column yielded a third white solid, which was identified as the 1,3-adamantane dinitrile (**3-30a**), $C_{10}H_{14}$[CN]$_2$, (0.7 g, 3.7 mmol, 21%), which was recrystallized from ethyl acetate to give clear colorless plate-shaped crystals, m.p. 186-187°C; IR (cm^{-1}): 2233 (m). NMR, ^{1}H δ: 2.30(s, 2H), 2.20(m, 2H), 2.04(m, 8H), 1.73(m, 2H); ^{13}C δ: 122.9 (C≡N), 40.9 (C_{quat}), 38.0 (CH_2), 33.6 (CH), 29.5 (CH_2), 26.0 (CH_2); MS [IE, 70eV] *m/z* (%): 186 (43, M$^+$), 159 (100, M$^+$-HCN), 118 (30).

3.2.4 Preparation of 1,8-Bis(1',3',4'-oxathiazol-2'-one-5'-yl)-octane, 3-28b, 1-Cyano-8-(1',3',4'-oxathiazol-2'-one-5'-yl)-octane, 3-29b, and Sebacanitrile, 3-30b

Chlorocarbonylsulfenyl chloride, ClSC(O)Cl, (5.24 g, 40 mmol) was added to a

mixture of toluene (50 mL) and sebacamide, $H_2N(O)C(CH_2)_8C(O)NH_2$, (2.0 g, 10 mmol), under nitrogen to give a clear yellow solution over a white solid. The solution was heated at 90-100 °C for 17.5 hr. The resulting clear brown solution was subjected to rotary evaporation (60°C water bath) and then vacuum (10^{-2}-10^{-3} mmHg) evaporation (at room temperature) to remove the excess ClSC(O)Cl and solvent, and a wet yellow solid (3.0 g) was obtained. The mixture was dissolved in $CHCl_3$ and passed through a column (silica gel, 240–400 mesh) to give a white solid 1,8-bis(1',3',4'-oxathiazol-2'-one-5'-yl)-octane (**3-28b**) (1.6 g, 5.1 mmol, 51%). This solid was recrystallised from $CHCl_3$ to give clear colorless needle shaped crystals, m.p. 112-114°C (dec. >114°C), UV-vis [λ_{max}(hexane)/nm (ε/dm^{3}mol^{-1}cm^{-1})]: 213 (7,700); IR (cm^{-1}): 1836 (w), 1765 (s), 1736 (s), 1625 (s), 1596 (ms), 1291 (ms), 1215 (m), 1171 (s), 1032(s), 918 (s), 721 (s), 651 (m). NMR, ^{1}H δ: 2.61(t, 4H, J = 7.5 Hz), 1.74-1.64 (m, 4H), 1.33 (m, 8H); ^{13}C δ: 174.3 (C=O), 161.8 (C_{sec}), 30.3 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 25.2 (CH_2); MS [IE, 70eV] *m/z* (%): 316 (0.5, M$^+$), 272 (1, [NS(O)COC]$(CH_2)_8$-CNS), 242 (5, [NS(O)COC]$(CH_2)_8$-CN), 198 (26, SNC-$(CH_2)_8$-CO), 166 (46, NC-$(CH_2)_8$-CO), 83 (97, C_6H_{11}), 55 (100, C_4H_7), 41 (98, C_3H_3),. Anal. calcd.: C 45.56, H 5.10, N 8.85%; found: C 45.65, H 4.96, N 8.85%.

A white solid mixture of 1-cyano-8-(1',3',4'-oxathiazol-2'-one-5'-yl)-octane (**3-29b**) and sebacanitrile (**3-30b**) was also obtained from the column. Attempts to isolate pure (**3-29b**) and (**3-30b**) were not successful.

3.2.5 Attempted Preparation of Bis(1',3',4'-oxathiazol-2'-one-5'-yl)methane, 3-28c

Chlorocarbonylsulfenyl chloride, ClSC(O)Cl, (13.2 g, 100 mmol) was added to a

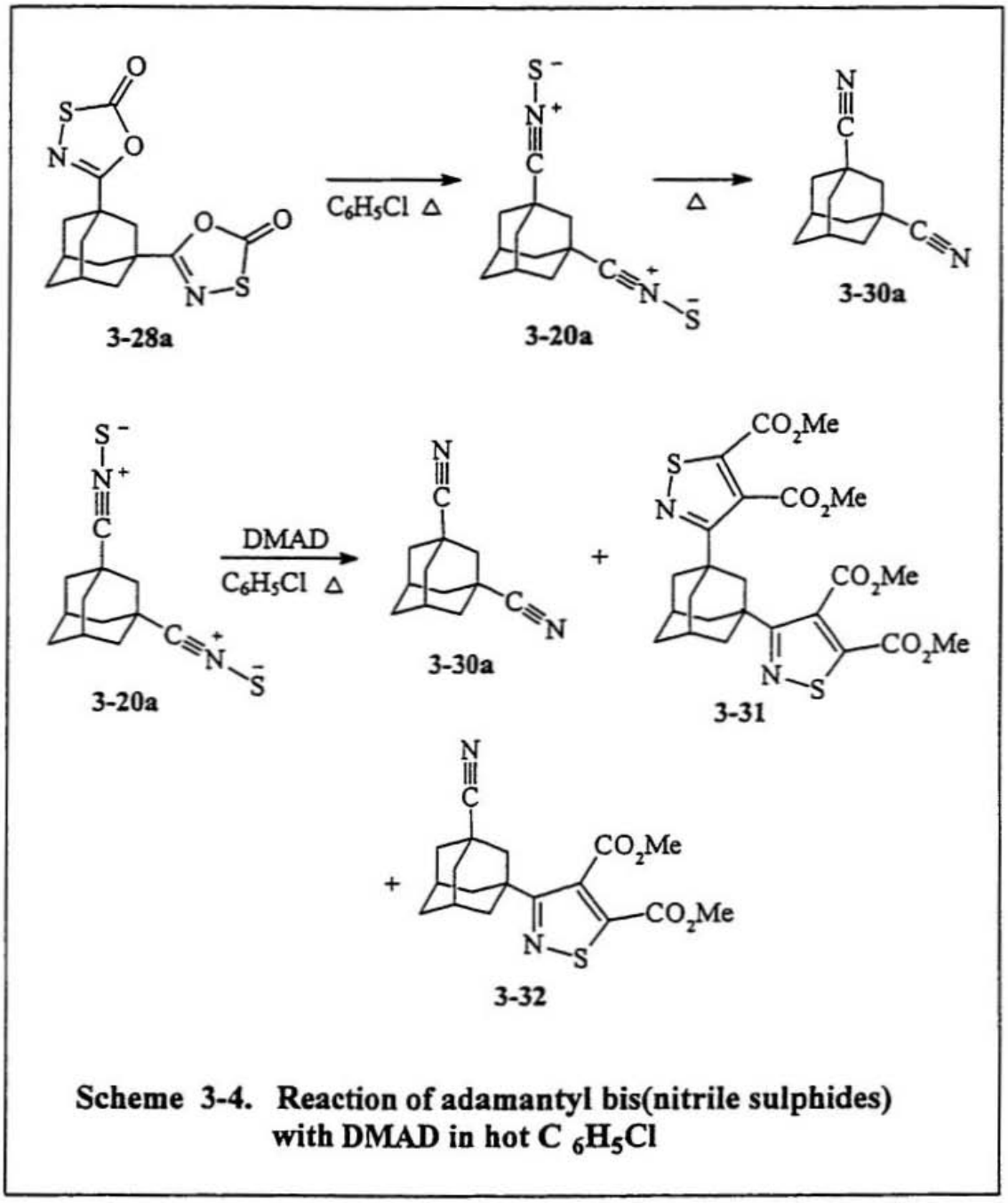
mixture of toluene (90 mL) and malonamide, $H_2N(O)CCH_2C(O)NH_2$, (2.6 g, 25 mmol), under nitrogen to give a clear yellow solution over a white solid. The solution was heated at 90-100 °C for 12 hours. The resulting dark brown solution was separated from the solid by a gravity filtration and then evaporated to give only a small amount of sulphur. The solid was identified as the unreacted malonamide by IR and its melting point.

3.2.6 Attempted Preparation of 1,4-Bis(1',3',4'-oxathiazol-2'-one-5'-yl) benzene, 3-28d

Chlorocarbonylsulfenyl chloride, ClSC(O)Cl, (13.6 g, 104 mmol) was added to a mixture of toluene (60 mL) and 1,4-benzenedicarbonamide, $H_2N(O)CC_6H_4C(O)NH_2$, (2.6 g, 25 mmol), (which was made from terephthalic acid by standard procedures[67]) under nitrogen to give a clear yellow solution over a white solid. The solution was heated at 90-100 °C for 72 hr. The resulting dark brown solution was separated from the solid by regular filtration and then evaporated to give only a small amount of sulphur. The solid was identified as the unreacted 1,4-benzenedicarbonamide by IR and its melting point.

3.2.7 Reaction of 1,3-Bis(1',3',4'-oxathiazol-2'-one-5'-yl)adamantane and DMAD

1,3-Bis(1',3',4'-oxathiazol-2'-one-5'-yl)-adamantane **(3-28a)** (2.3 g, 6.8 mmol) and MeO_2CCCCO_2Me, DMAD (1.5 g 11 mmol) were dissolved in chlorobenzene (50 mL). The slightly yellow clear solution turned brown and evolved a gas while it was heated to reflux. The heating was stopped after 12 hr at which point the solution was a clear dark red-brown. An oily dark brown solid (6.1 g) was obtained after the solvent was removed. The solid was dissolved in $CHCl_3$ and passed through a column (silica gel 240-400 mesh)



Scheme 3-4. Reaction of adamantyl bis(nitrile sulphides) with DMAD in hot C $_6$H$_5$Cl

to give an oily orange solid (5.5 g). The orange solid was loaded on a Kugelrohr distillation apparatus, and heated at 110°C to remove the by-products: tetramethyl thiophenetetracarboxylate and S_8 (total mass: 0.2 g). The temperature was then raised to 165°C to give the white solid, 1,3-adamantane-dinitrile (0.6 g, 44%), in the outer bulb and a purple sticky solid, 1-cyano-3-(4',5'-bis(methoxylcarbonyl)-isothiazol-3'-yl)-adamantane (**3-32**) (1.1 g, 44%), in the inner bulb. The compound (**3-32**) was recrystallized from ethyl acetate to give clear colorless plate-shaped crystals, m.p. 87-88°C, UV-vis [λ_{max}(hexane)/nm (ε/dm^{3}mol^{-1}cm^{-1})]: 277 (6,600), 231 (7,000), 191 (21,000); IR (cm^{-1}): 2232 (w), 1737 (ms), 1706 (ms), 1528 (m), 1286 (s), 1252 (s), 1145 (m), 1052(m), 915 (w), 809(w), 773 (w). NMR, ^{1}H δ: 3.97/3.92 (s, 6H), 2.37 (s, 2H), 2.22 (m, 2H), 2.05 (m, 8H), 1.74 (m, 2H); ^{13}C δ: 172.7 (C=O), 165.9 (C=O), 159.3 (C_{het}), 155.4 (C_{het}), 132.4 (C_{het}), 124.3 (C≡N), 53.1/52.9 (OMe), 42.4 (CH_2), 39.6 (C_{quat}), 39.0 (CH_2), 38.7 (CH_2), 34.5 (CH_{quat}) 30.7 (CH_2), 27.3 (CH); MS [IE, 70eV] *m/e* (%): 360 (49, M$^+$), 345 (100, M - Me), 328 (31, M - MeOH), 300 (26, M - HCO_2Me), 270 (46, NC-$C_{10}H_{14}$-[CCCSN]-CO), 186 (2, NC-$C_{10}H_{14}$-CN), 160 (4, $C_{10}H_{14}$-CN). Anal. calcd.: C 60.0, H 5.6, N 7.8; found: C 59.9, H 5.6, N 7.9.

The brown sticky solid residue from above was shown to be 1,3-bis(4',5'-bis(methoxylcarbonyl)-isothiazol-3'-yl)-adamantane (**3-31**) (0.45 g, 12%). Clear colorless parallelepiped crystals were recrystallized from ethyl acetate, m.p. 149-150°C, UV-vis [λ_{max}(hexane)/nm (ε/dm^{3}mol^{-1}cm^{-1})]: 278 (7,400), 229 (8,700), 191 (31,000); IR (cm^{-1}): 1972 (w), 1933 (w), 1896 (w), 1871 (w), 1803 (w), 1772 (ms), 1742 (ms), 1595 (ms),

1262 (ms), 1221 (ms), 1084(m), 973 (ms), 919(ms). NMR, ^{1}H δ: 3.97/3.91 (s, 6H), 2.43 (s, 2H), 2.26 (m, 2H), 2.12-2.00 (m, 8H), 1.76 (m, 2H); ^{13}C δ: 174.1 (C=O), 165.9 (C=O), 159.2 (C_{het}), 154.7 (C_{het}), 132.6 (C_{het}), 53.0/52.8 (OMe), 43.8 (CH_2), 40.9 (C_{quat}), 39.6 (CH_2), 35.1 (CH_2), 28.5 (CH); MS [IE, 70eV] *m/e* (%): 534 (100, M^+), 519 (100, M - Me), 503 (24, M - OMe), 502 (12, M - MeOH), 487 (17, M - MeOH, Me), 470 (13, M - 2S), 416 (14, M - $2CO_2CH_3$). Anal. calcd.: C 53.9, H 4.9, N 5.2; found: C 53.7, H 4.9, N 5.2.

3.2.8 Reaction of 1,3-Bis(1',3',4'-oxathiazol-2'-one-5'-yl)adamantane and 1,3-Adamantane Dinitrile

1,3-Bis(1',3',4'-oxathiazol-2'-one-5'-yl)adamantane (**3-28a**) (0.27 g, 0.8 mmol) and 1,3-adamantane dinitrile $C_{10}H_{14}(CN)_2$ (0.15 g, 0.8 mmol) were dissolved in chlorobenzene (6 mL) and heated to reflux for 4 hr. The initially clear colorless solution turned to a clear brown. The ^{13}C NMR spectrum (δ ppm, in $CDCl_3$) of the starting materials mixture (molar ratio 1:1) showed 13 peaks [174.1 (C=O), 165.5 (C=N), 122.9 (C≡N), 41.1, 39.7, 38.4, 38.2, 37.8, 34.6, 33.8, 29.6, 27.1, 26.1] (Appendix 3). The solvent was removed and the resulting solid residue was dried under vacuum. The ^{13}C NMR spectrum (δ ppm) of the residue redissolved in $CDCl_3$ showed six peaks [122.8 (C≡N), 40.7, 37.9, 33.4, 29.4, 25.9] of the reaction residue (Appendix 3).

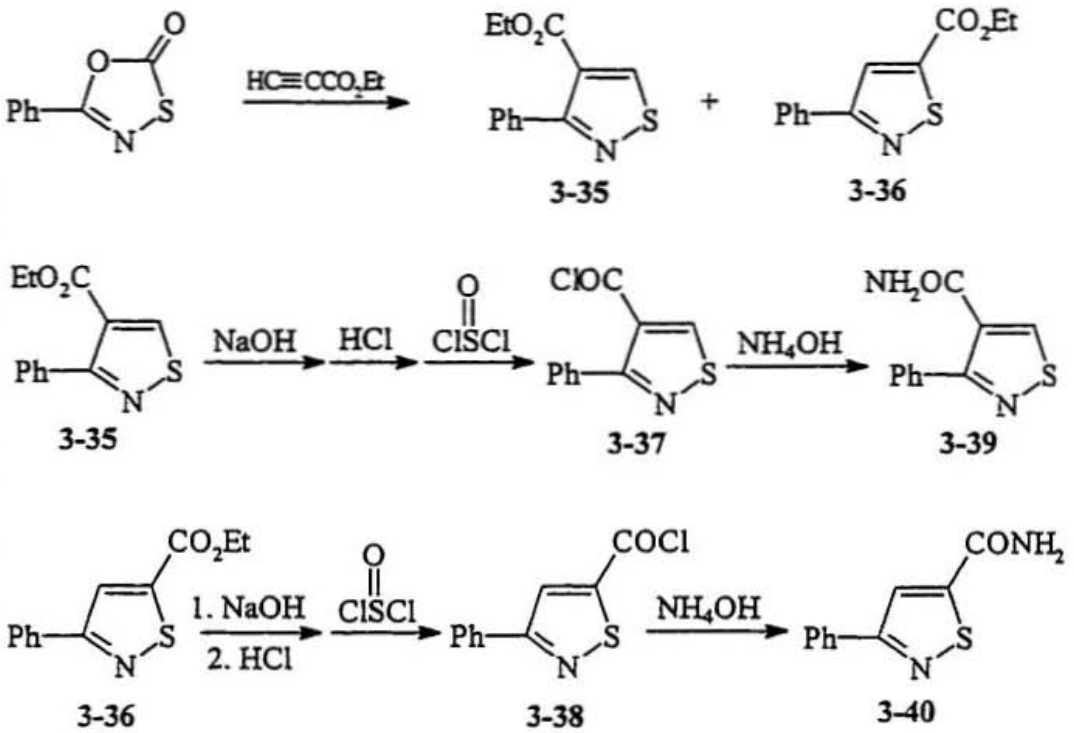
3.2.9 Preparation of 3-Phenyl-isothiazole-4/5-carbonyl chloride and 3-Phenyl-isothiazole-4/5-carbonamide

The mixture of 3-phenyl-isothiazole-4/5-carboxylic acid which was made from

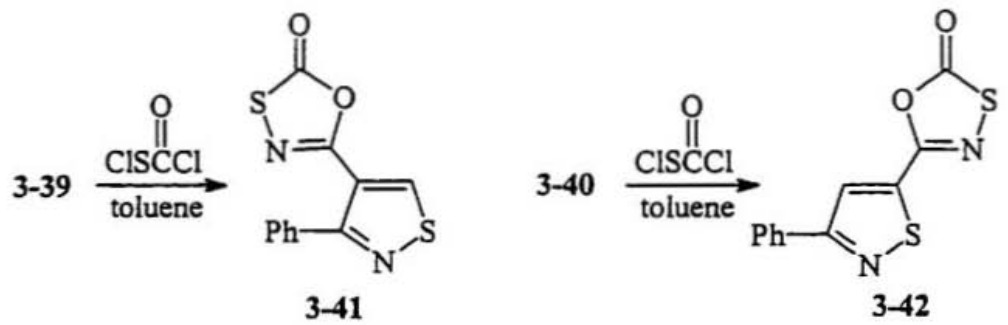
ethyl 3-phenyl-isothiazole-4/5-carboxylate (**3-35**)/(**3-36**) by following the literature procedure[14], (25 mmol), and thionyl chloride (~50 mL) was heated to reflux for 3 hours. The excess thionyl chloride was removed by regular distillation and a white solid was obtained and dried under vacuum. The crude product 3-phenyl-isothiazole-4/5-carboxylic chloride (**3-37**)/(**3-38**) was mixed *in situ* with NH_4OH under nitrogen. The mixture was then heated to reflux for 4 hr. Shiny colorless crystals, 3-phenyl-isothiazole-4-carbonamide (**3-39**), were obtained when it was recrystallised from $CHCl_3$ (3.2 g, 62%), m.p. 138-140°C; IR (cm^{-1}): 3369 (s), 3183 (s), 3082 (m), 1639 (s), 1622 (s), 1502 (w), 1214 (m), 1120 (m), 709 (ms), 694(m). MS [IE, 70eV] *m/e* (%): 204 (79, M^+), 203 (100, M - 1), 188 (56, M - NH_2), 160 (11, M - $CONH_2$), 135 (3, M - $HC{\equiv}CCONH_2$), 103 (6, C_6H_5CN), 77 (25, C_6H_5); Nice shiny white crystals of 3-phenyl-isothiazole-5-carbonamide (**3-40**) were obtained when the reaction solution was cooled down (4.2 g, 83%), m.p. 148-149°C; IR (cm^{-1}): 3334 (s), 3180 (s), 3099 (m), 3064 (ms), 1649 (s), 1531 (ms), 1500 (ms), 1415 (s), 1122 (ms), 1128 (ms), 850 (ms), 763 (s), 685(s). NMR, ^1H δ: 3.48 (s, 2H), 7.42-7.53 (m, 3H), 7.93-7.96 (m, 2H), 8.38 (s, 1H); ^{13}C δ: 167.9 (C=O), 164.6, 160.9, 134.0, 129.8, 129.2, 126.6, 121.7; MS [IE, 70eV] *m/e* (%): 204 (100, M^+), 188 (64, M - NH_2), 160 (9, M - $CONH_2$), 135 (3, M - $HC{\equiv}CCONH_2$).

3.2.10 Preparation of 5-(3'-Phenyl-isothiazol-4'-yl)-1,3,4-oxathiazol-2-one

Chlorocarbonylsulfenyl chloride, ClSC(O)Cl, (4.2 g, 32 mmol) was added to a mixture of toluene (40 mL) and 3-phenyl-isothiazole-4-carbonamide, (**3-39**), (2.9 g, 14 mmol), under nitrogen to give a clear yellow solution over a white solid. The solution



Scheme 3-5. Preparation of phenyl isothiazolyl carbonamides



Scheme 3-6. Preparation of phenyl isothiazolyl oxathiazolones

was heated at 90-100 °C for 1.5 hr. The resulting clear brown solution was allowed to naturally evaporate (at room temperature) to remove the excess ClSC(O)Cl and solvent, and a yellowish white solid was obtained. This solid was recrystallised from toluene to give clear colorless needle shaped crystals of 3-phenyl-4-(1',3',4'-oxathiazol-2'-one-5'-yl)-isothiazole (**3-41**) (3.2 g, 86%), m.p. 142°C (dec.), UV-vis [λ_{max}(hexane)/nm (ε/dm^{3}mol^{-1}cm^{-1})]: 275-230 (broad, 13,000), 197 (53,000); IR (cm^{-1}): 3100 (w), 1812 (w), 1749 (s), 1735 (s), 1598 (s), 1182 (m), 1088(m), 1014 (w), 959 (s), 884 (ms), 834 (ms), 765 (s), 734 (s), 692 (ms). NMR, ^{1}H δ: 9.28(s, 1H), 7.61 (m, 2H), 7.46 (m, 3H); ^{13}C δ: 172.7, 161.8, 154.1, 152.1, 134.0, 129.6, 129.0, 128.2, 123.3; MS [IE, 70eV] ***m/z*** (%): 262 (22, M$^+$), 218 (2, M - CO_2), 188 (78, M - CONS), 186 (100, C_6H_5[CCCNS]-CN), 160 (13, M - COCONS), 135 (26, C_6H_5CNS), 103 (13, C_6H_5CN), 77 (29, C_6H_5). Anal. calcd.: C 50.37, H 2.31, N 10.68%; found: C 50.22, H 2.40 N 10.68%.

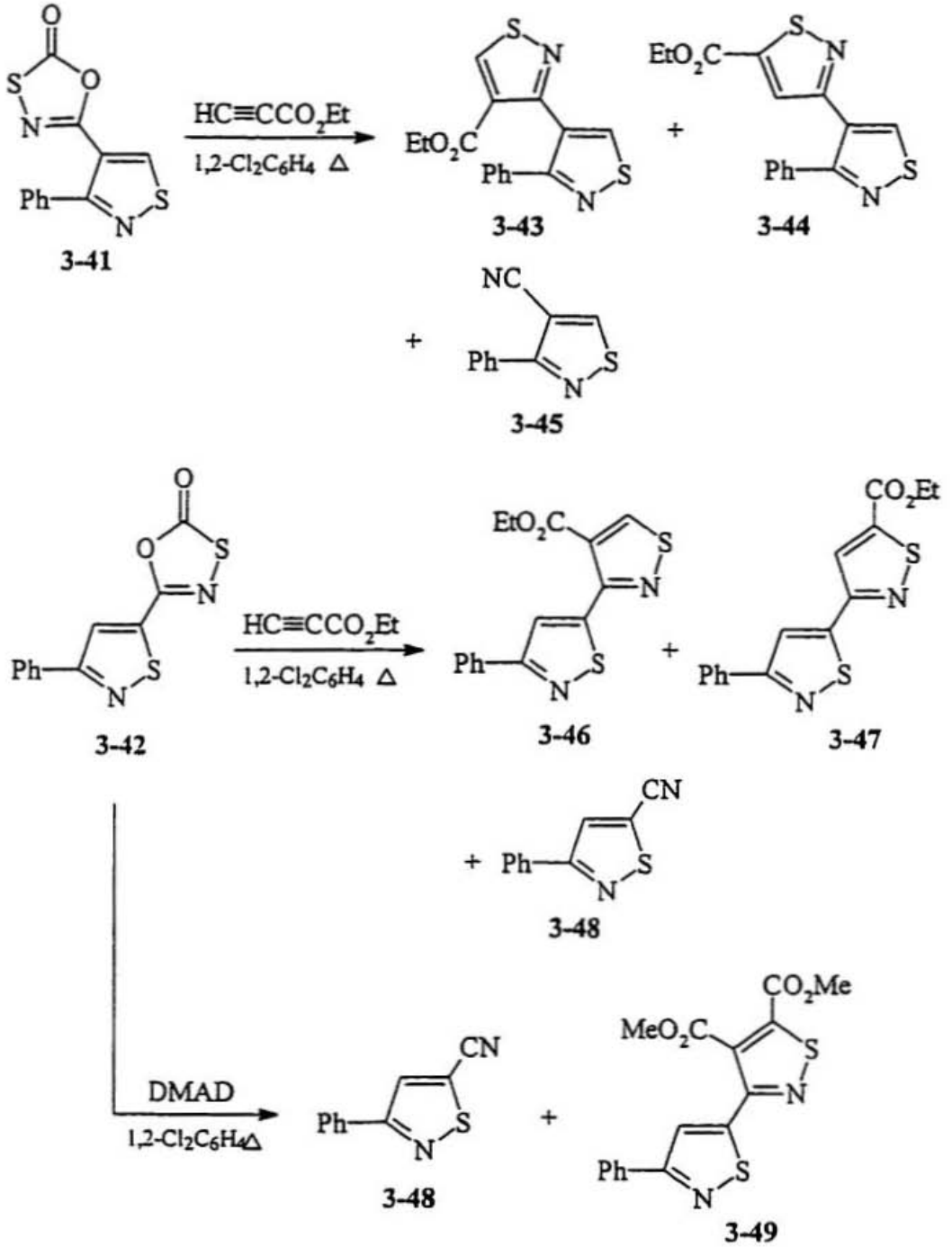
3.2.11 Preparation of 5-(3'-Phenyl-isothiazol-5'-yl)-1,3,4-oxathiazol-2-one

Chlorocarbonylsulfenyl chloride, ClSC(O)Cl, (6.5 g, 50 mmol) was added to a mixture of toluene (50 mL) and 3-phenyl-isothiazole-5-carbonamide, (**3-40**), (4.1 g, 20 mmol), under nitrogen to give a clear yellow solution over a white solid. The solution was heated at 90-100 °C for 8.5 hr. The resulting clear greenish yellow solution was subjected to natural evaporation (at room temperature) to remove the excess ClSC(O)Cl and solvent, and a white solid was obtained. This solid was recrystallised from toluene to give clear colorless needle shaped crystals of 3-phenyl-5-(1',3',4'-oxathiazol-2'-one-5'-yl)-isothiazole (**3-42**) (5.2 g, 100%), m.p. 129-130°C, UV-vis [λ_{max}(hexane)/nm

(ε/dm^{3}mol^{-1}cm^{-1})]: 283 (18,000), 248 (23,000), 203 (31,000); IR (cm^{-1}): 3097 (w), 3066 (w), 3032 (w), 1813 (ms), 1759 (s), 1738 (s), 1600 (ms), 1598 (ms), 1517 (s), 1496 (s), 1055 (ms), 973 (s), 902 (s), 776 (s), 695 (s). NMR, ^{1}H δ: 7.98 (s, 1H), 7.91-7.94 (m, 2H), 7.42-7.49 (m, 3H); ^{13}C δ: 171.5, 167.9, 150.7, 150.5, 133.4, 129.9, 128.9, 126.8, 122.5; MS [IE, 70eV] *m/z* (%): 262 (52, M$^+$), 218 (3, M - CO_2), 188 (100, M - CONS), 160 (9, M - COCONS), 135 (2, C_6H_5CNS). Anal. calcd.: C 50.37, H 2.31, N 10.68%; found: C 49.84, H 2.41 N 10.50%.

3.2.12 Reaction of 5-(3'-Phenyl-isothiazol-4'-yl)-1,3,4-oxathiazol-2-one and Ethyl Propiolate

The 3-phenyl-4-(1',3',4'-oxathiazol-2'-one-5'-yl)-isothiazole (**3-41**) (1.8 g, 6.8 mmol) and ethyl propiolate (2.7 g, 27 mmol) were dissolved in *o*-dichlorobenzene (30 mL). The clear colorless solution was heated to reflux for 2 hr to give a red brown solution. The excess ethyl propiolate and solvent were removed by rotary evaporation (90°C water bath). The crude product was redissolved in $CHCl_3$ and passed through a column (silica gel, mesh 320-400) with benzene to give 3-phenyl-4-cyano-isothiazole (**3-45**) (0.7 g, 55%), m.p. 49-50°C, IR (cm^{-1}): 3096 (w), 2232 (w), 1489 (s), 1446 (ms), 1407 (s), 1333 (w), 1220 (w), 1076 (w), 1006 (w), 872 (m), 813 (m), 774 (s), 693 (s). NMR, ^{1}H δ: 9.23 (s, 1H), 8.03 (m, 2H), 7.48 (m, 3H); ^{13}C δ: 167.1, 158.6, 132.1, 130.3, 128.7, 127.5, 113.7, 107.1; MS [IE, 70eV] *m/z* (%): 186 (100, M$^+$), 160 (7, M - CN), 135 (20, C_6H_5CNS), 103 (8, C_6H_5CN), 77 (15). Anal. calcd.: C 64.50, H 3.25, N 15.04%; found: C 64.11, H 3.38, N 14.92%.



Scheme 3-7. Reactions for phenyl isothiazolyl oxathiazolones 3-41/42

A second white solid was also obtained from the column, ethyl 3-(3'-phenyl-isothiazol-4'-yl)-isothiazole-4-carboxylate (0.7 g, 33%) (**3-43**), m.p. 94-95°C, UV-vis [λ_{max}(hexane)/nm (ε/dm^{3}mol^{-1}cm^{-1})]: 265 (69,000), 195 (40,000); IR (cm^{-1}): 3105 (m), 3069 (m), 1696 (s), 1535 (w), 1493 (ms), 1298 (m), 1256 (s), 1211 (m), 1166 (m), 1094 (m), 1051 (m), 860 (m), 840 (m), 770 (ms), 732 (m), 703 (ms). NMR, ^{1}H δ: 9.28 (s, 1H), 8.83 (s, 1H), 7.29 (m, 5H), 3.92 (q, J = 7.1 Hz, 2H), 1.03 (t, J = 7.1 Hz, 3H); ^{13}C δ: 166.5, 162.2, 160.8, 155.5, 149.4, 134.9, 131.9, 130.6, 128.7, 128.3, 127.8, 61.0, 13.7; MS [IE, 70eV] *m/z* (%): 316 (44, M$^+$), 315 (100, M - 1), 287 (24 M - C_2H_5), 271 (9, M - OEt), 243 (47, M - $C_3H_5O_2$), 185 (2, Ph[CCCNS]-CN - 1), 160 (1, Ph[CCCNS]), 135 (5, Ph-CNS), 103 (5, PhCN), 77 (12). Anal. calcd.: C 56.94, H 3.82, N 8.85%; found: C 56.63, H 3.92, N 8.88%.

A third yellow-brown oily solid (impure) was recovered from the column and was identified as ethyl 3-(3'-phenyl-isothiazol-4'-yl)-isothiazole-5-carboxylate (0.3 g, 14%) (**3-44**), IR (cm^{-1}): 3100 (m), 3062 (m), 1724 (s), 1540 (m), 1514 (m), 1499 (m), 1466 (m), 1432 (m), 1369 (m), 1341 (ms), 1238 (s), 1089 (ms), 1012 (m), 864 (ms), 805 (ms), 755 (ms), 730 (m), 698 (ms). NMR, ^{1}H δ: 9.08 (s, 1H), 7.41 (m, 5H), 4.36 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C δ: 165.9, 161.8, 159.3, 157.2, 150.1, 134.5, 132.0, 129.0, 128.5, 128.2, 126.8, 61.9, 13.9; MS [IE, 70eV] *m/z* (%): 316 (37, M$^+$), 315 (100, M - 1), 287 (63, M - C_2H_5), 271 (7, M - OEt), 243 (33, M - $C_3H_5O_2$), 185 (8, Ph[CCCNS]-CN - 1), 160 (2, Ph[CCCNS]), 135 (6, Ph-CNS), 103 (6, PhCN), 77 (14).

3.2.13 Reaction of 5-(3'-Phenyl-isothiazol-5'-yl)-1,3,4-oxathiazol-2-one and Ethyl

Propiolate

The 3-phenyl-5-(1',3',4'-oxathiazol-2'-one-5'-yl)-isothiazole (**3-42**) (1.8 g, 6.8 mmol) and ethyl propiolate (2.7 g, 28 mmol) were dissolved in *o*-dichlorobenzene (20 mL). The clear colorless solution was heated to reflux for 3 hr. to give a red brown solution. The excess ethyl propiolate and solvent were removed by rotary evaporation (90°C water bath). The crude product was redissolved in $CHCl_3$ and passed through a column (silica gel, mesh 320-400) with benzene to give 3-phenyl-5-cyano-isothiazole (**3-48**) (0.2 g, 16%), m.p. 78-79°C, IR (cm^{-1}): 3097 (w), 2227 (w), 1965 (w), 1897 (w), 1613 (w), 1762 (w), 1687 (w), 1600 (w), 1519 (w), 1496 (m), 1304 (w), 1284 (w), 1214 (w), 1109 (w), 1084 (w), 890 (ms), 841 (s), 768 (s), 690 (s). NMR, ^1H δ: 7.97 (s, 1H), 7.90 (m, 2H), 7.48-7.46 (m, 3H); ^{13}C δ: 167.8, 134.0, 132.8, 130.3, 129.1, 128.6, 127.0, 110.9; MS [IE, 70eV] *m/z* (%): 186 (100, M^+), 159 (16, M - HCN), 135 (10, C_6H_5CNS), 103 (9, C_6H_5CN), 77 (20). Anal. calcd.: C 64.50, H 3.25, N 15.04%; found: C 64.12, H 3.17, N 14.80%.

A second white solid was also obtained from the column, ethyl 3-(3'-phenyl-isothiazol-5'-yl)-isothiazole-4-carboxylate (0.8 g, 37%) (**3-46**), m.p. 122-123°C, UV-vis [λ_{max}(hexane)/nm ($\varepsilon/dm^3mol^{-1}cm^{-1}$)]: 277 (21,000), 255 (26,000), 203 (31,000); IR (cm^{-1}): 3142 (w), 3076 (w), 1721 (s), 1583 (w), 1541 (w), 1291 (m), 1238 (s), 1181 (m), 1167 (m), 1092 (m), 1079 (s), 860 (ms), 766 (s), 722 (m), 659 (m). NMR, ^1H δ: 9.34 (s, 1H), 8.48 (s, 1H), 8.02-8.00 (m, 2H), 7.48-7.38 (m, 3H), 4.41-4.34 (q, J = 7.1 Hz, 2H), 1.40-1.35 (t, J = 7.1 Hz, 3H); ^{13}C δ: 166.8, 161.3, 159.8, 158.1, 156.9, 134.6, 129.0, 128.6,

128.1, 126.7, 122.5, 61.6, 14.2; MS [IE, 70eV] *m/z* (%): 316 (100, M^+), 288 (9, M - C_2H_4), 271 (21, M - OEt), 244 (20, M - $C_3H_4O_2$), 186 (2, Ph[CCCNS]-CN), 135 (12, Ph-CNS), 77 (21). Anal. calcd.: C 56.94, H 3.82, N 8.85%; found: C 57.26, H 3.93, N 9.05%.

A third white solid was recovered from the column and was identified as ethyl 3-(3'-phenyl-isothiazol-5'-yl)-isothiazole-5-carboxylate (0.8 g, 37%) (**3-47**), m.p. 117-118°C, UV-vis [λ_{max}(hexane)/nm (ε/dm^{3}mol^{-1}cm^{-1})]: 298 (17,000), 246 (36,000), 202 (33,000); IR (cm^{-1}): 3076 (w), 1719 (s), 1551 (w), 1516 (w), 1252 (s), 1083 (m), 1027 (m), 885 (m), 857 (s), 811 (m), 769 (s), 696 (m). NMR, ^{1}H δ: 7.95 (s, 1H), 7.94-7.91 (m, 2H), 7.82 (s, 1H), 7.45-7.37 (m, 3H), 4.42-4.35 (q, J = 7.1 Hz, 2H), 1.42-1.37 (t, J = 7.1 Hz, 3H); ^{13}C δ: 167.9, 160.4, 159.2, 158.9, 158.5, 134.1, 129.2, 128.6, 126.6, 124.7, 119.1, 62.2, 14.0; MS [IE, 70eV] *m/z* (%): 316 (100, M^+), 288 (23, M - C_2H_4), 271 (12, M - OEt), 243 (6, M - $C_3H_5O_2$), 186 (8, Ph[CCCNS]-CN), 160 (3, Ph[CCCNS]), 135 (14, Ph-CNS), 77 (12). Anal. calcd.: C 56.94, H 3.82, N 8.85%; found: C 56.76, H 3.66, N 8.81%.

3.2.14 Reaction of 5-(3'-Phenyl-isothiazol-5'-yl)-1,3,4-oxathiazol-2-one and DMAD

The oxathiazolone (**3-42**) (2.6 g, 10 mmol) and DMAD (5.5 g, 39 mmol) were dissolved in *o*-dichlorobenzene (40 mL). The clear colorless solution was heated to reflux for 3 hr. to give a red brown solution. The excess ethyl propiolate and solvent were removed by rotary evaporation (90°C water bath). The crude product was redissolved in $CHCl_3$ and passed through a column (silica gel, mesh 320-400) to give the unreacted

oxathiazolone (**3-42**) (0.65 g, 22%) and the desired product 3-phenyl-5-(dimethyl 4',5'-isothiazoledicarboxylate-3'-yl)-isothiazole (**3-49**) (2.9 g, 78%) m.p. 122-124°C, UV-vis [λ_{max}(hexane)/nm (ε/dm^{3}mol^{-1}cm^{-1})]: 296 (9,300), 248 (2,500), 202 (2,600); IR (cm^{-1}): 1735 (s), 1726 (s), 1530 (m), 1277 (s), 1263 (s), 1243 (s), 1136 (m), 1068 (m), 1007 (m), 960 (m), 878 (m), 802 (m), 771 (ms), 728 (ms), 692 (m). NMR, ^{1}H δ: 7.93-7.96 (m, 2H), 7.89 (s, 1H), 7.41-7.49 (m, 3H), 4.04 (s, 3H), 3.96 (s, 3H); ^{13}C δ: 167.8, 163.9, 158.9, 158.7, 156.6, 156.3, 134.2, 131.5, 129.4, 128.8, 126.8, 120.0, 53.6, 53.4; MS [IE, 70eV] *m/z* (%): 360 (100, M$^+$), 345 (3, M - Me), 329 (40, M - OMe), 186 (21, M - DMAD). Anal. calcd.: C 53.32, H 3.36, N 7.77%; found: C 52.97, H 3.41, N 7.75%.

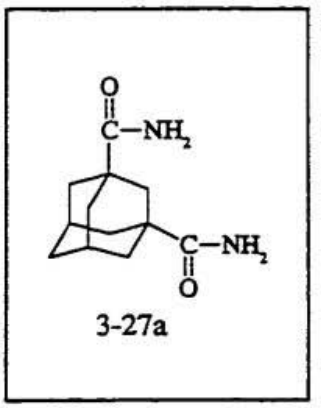
3.2.15 Decomposition Temperatures of Oxathiazolones

Separate samples of 5-adamantyl-1,3,4-oxathiazol-2-one **2-30**, 5-phenyl-1,3,4-oxathiazol-2-one, 3-phenyl-5-(1',3',4'-oxathiazol-2'-one-3'-one-3'-yl)-isothiazole **3-42** (1 mmol) were dissolved in 10 ml of solvent (chlorobenzene or *o*-dichlorobenzene). The solution was heated in an oil bath from 50°C to 180°C in increments of 10°C with thermal equilibration for an hour at each temperature. The solution IR spectrum of samples withdrawn from this solution at each temperature interval were recorded at room temperature. The C=O and C≡N stretching frequencies were monitored and the decomposition temperature was defined as at which the C=O absorption decreased at least 50% in intensity between measurements. The following decomposition temperatures were determined: 5-adamantyl-1,3,4-oxathiazol-2-one **2-30** (110°C), 5-phenyl-1,3,4-oxathiazol-2-one (120°C), 3-phenyl-5-(1',3',4'-oxathiazol-2'-one-3'-yl)-isothiazole **3-42** (160°C).

3.3 Results and Discussion

3.3.1 Preparation and Structure of 1,3-Adamantanedicarbonamide

1,3-Adamantanedicarbonamide **3-27a** has been reported previously[98] but has not been reported in many synthetic schemes[99]. The structure of this compound has not been described although some structures of similar adamantane based derivatives have been reported before[100]. The dicarbonamide **3-27a** was prepared from 1,3-adamantane dicarbonyl chloride using a variation of the preparation described in ref. 98. The 1,3-adamantane dicarbonyl chloride was made from 1,3-adamantane dicarboxylic acid by following the standard procedure[67]. The yield of the amide **3-27a** obtained here (94%) has been improved (reported 89%). The crystal structure of the compound was obtained (Fig. 3-8 and Fig. 3-9). The observed structure [bond distances and angles (Appendix 3)] of the adamantane moiety in **3-27a** is not significantly different [$\Delta D \leq 3\sigma$] from that reported for 1,3-adamantane dicarbonyl chloride[100]. The structure of the diacid chloride revealed a crystallographic mirror plane while compound **3-27a** was found to have a two fold axis. The tetracid derivative of adamantane has two strong hydrogen bonds to each substituent group[100]. The ORTEP view of the two dimensional network reveals that the solid state of the amide **3-27a** is a two dimensional sheet of monomer units held together throughout the whole crystal by hydrogen bonds.



3-27a

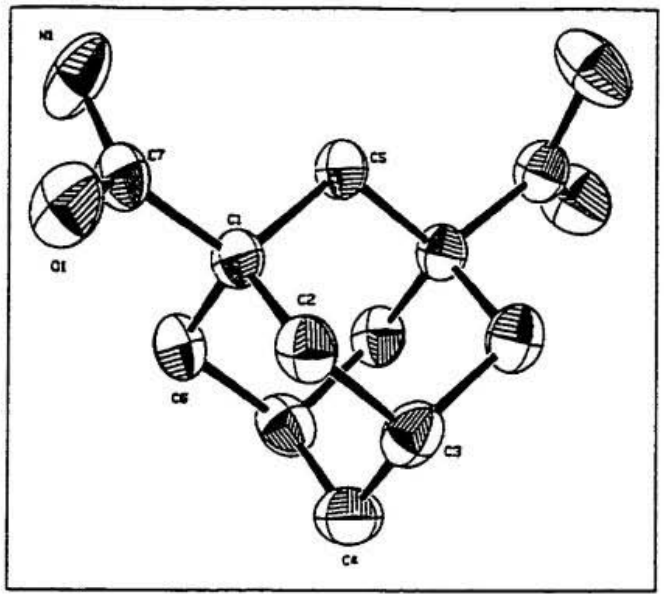


Figure 3-8 ORTEP view of 1,3-adamantanedicarbonamide **3-27a**

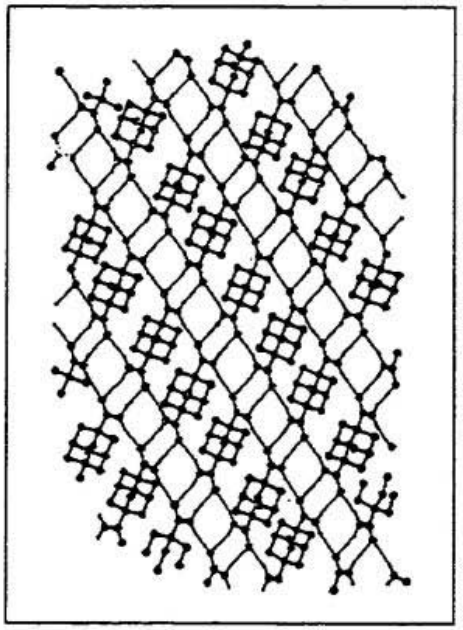
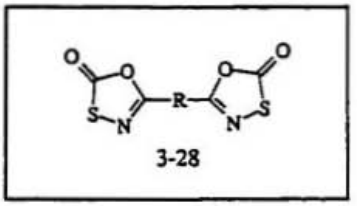


Figure 3-9 ORTEP view of 1,3-adamantanedicarbonamide **3-27a** (two dimensional network)

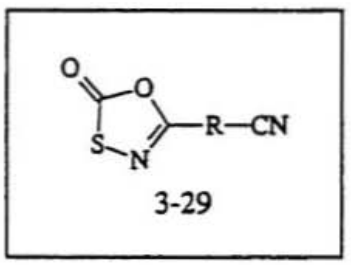
3.3.2 Preparation of Bis(oxathiazolones)

The reaction of carbonamides with chlorocarbonylsulfenyl chloride in hot toluene solutions have been reported to give 5-substituted-1,3,4-oxathiazol-2-ones **1-1** in varying yields[7,59]. All the compounds described in those reports contained only one oxathiazolone unit in the molecule and they were used as precursors for the thermal generation of the nitrile sulphides **1-2**. Müllbauer and Weiss claimed that they prepared derivatives of the bis(oxathiazolones) **3-28** (R = alkyl and aryl) from the reaction of $R[C(O)NH_2]_2$ with ClSC(O)Cl in their patent[101]. Only one example (R = CH_2CH_2) of the bis(oxathiazolones) was given in their claim and no detail about the reaction itself and the product was described or discussed.



3-28

In this work, the reactions of 1,3-adamantanedicarbonamide **3-27a** (1,3-$C_{10}H_{14}[C(O)NH_2]_2$), sebacamide **3-27b** ($H_2N(O)C(CH_2)_8C(O)NH_2$), malonamide **3-27c** ($H_2N(O)CCH_2C(O)NH_2$), and 1,4-benzenedicarbonamide **3-27d** (1,4-$C_6H_4[C(O)NH_2]_2$) with excess chlorocarbonylsulfenyl chloride have been investigated. Amides **3-27a** and **3-27b** reacted with chlorocarbonylsulfenyl chloride to give a mixture of products: bis(oxathiazolone) **3-28**, mono(nitrile)-mono(oxathiazolone) **3-29**, and the dinitrile **3-30** which is the thermal decomposition product from either **3-28** or **3-29**. These results are consistent with those from the reactions of the carbonamides with chlorocarbonylsulfenyl chloride



3-29

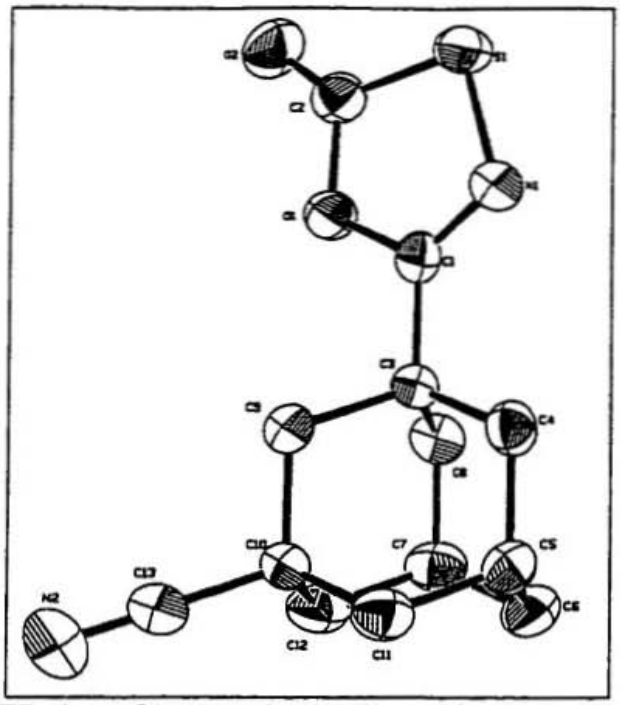


Figure 3-10 ORTEP view of 1-cyano-3-(1',3',4'-oxathiazol-2'-one-5'-yl)-adamantane **3-29a**

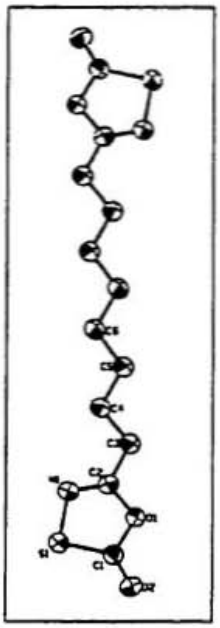
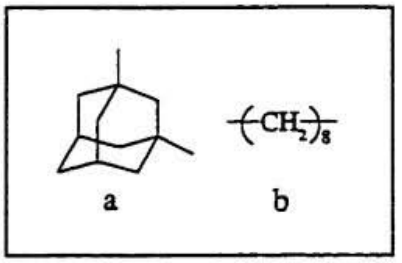


Figure 3-11 ORTEP view of 1,8-bis(1',3',4'-oxathiazol-2'-one-5'-yl)-octane **3-28b**

discussed in Chapter 2. The cycloadduct bis(oxathiazolones) **3-28** were recovered in 48% and 51% yield from 1,3-adamantanedicarbonamide **3-27a** and sebacamide **3-27b** respectively. The reaction of 1,3-adamantanedicarbonamide **3-27a** with ClSC(O)Cl gave the partial decomposition product, mono(oxathiazolone) **3-29a**, in 23% yield and the final decomposition product dinitrile **3-30a** in 21% yield. The total recovery of the adamantane based compound **3-27a** is approximately 92%. Unfortunately, column chromatography with a variety of solvent combinations did not give adequate separation of the mono(oxathiazolone) **3-29b** and the dinitrile **3-30b** from the reaction of sebacamide and ClSC(O)Cl. The compounds [**3-28a**, **3-28b**, **3-29a**] were clearly identified as oxathiazolone derivatives by the observation of distinctive ^{13}C NMR resonances in the regions 174.2 ± 0.6 ppm (**3-28a** 174.0 ppm, **3-29a** 173.7 ppm, **3-28b** 174.3 ppm, assigned to C=O) and 162 ± 5.2 ppm (**3-28a** 165.5 ppm, **3-29a** 164.7 ppm, **3-28b** 161.8 ppm, assigned to C=N). All three compounds were fully characterized spectroscopically and their structures were confirmed by X-ray crystallographic methods. The crystallographic data and selected bond lengths and angles for compounds **3-29a** and **3-28b** are listed in Appendix 2 (**3-28a** was originally reported by Schriver[102]). The 1,3-adamantanedinitrile **3-30a** (melting point, IR spectrum and elemental analysis) has been reported before[99]. The compound (recrystallized from ethyl acetate) generated from this work has a much lower melting point 186-187°C than the literature 199-200°C



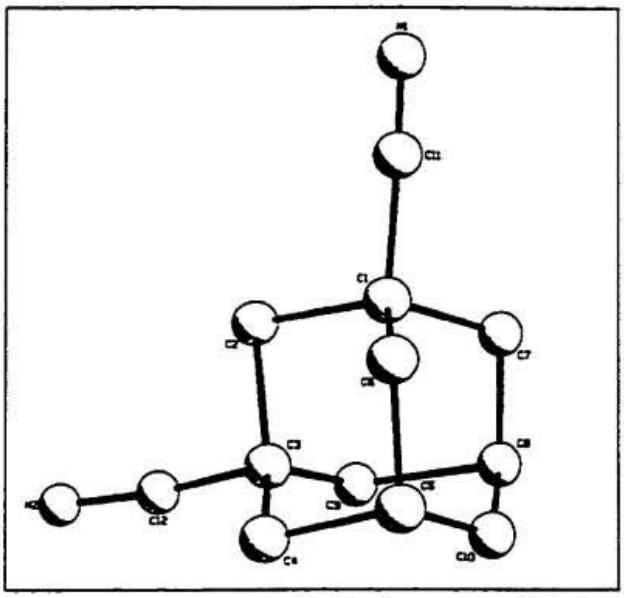


Figure 3-12 Structure of 1,3-adamantanedinitrile **3-30a**

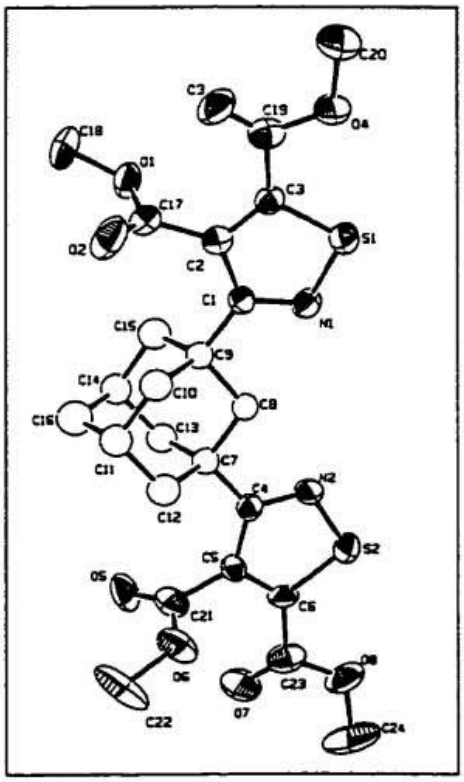


Figure 3-13 ORTEP view of 1,3-bis(4',5'-bis(methoxylcarbonyl)-isothiazol-3'-yl)-adamantane **3-31**

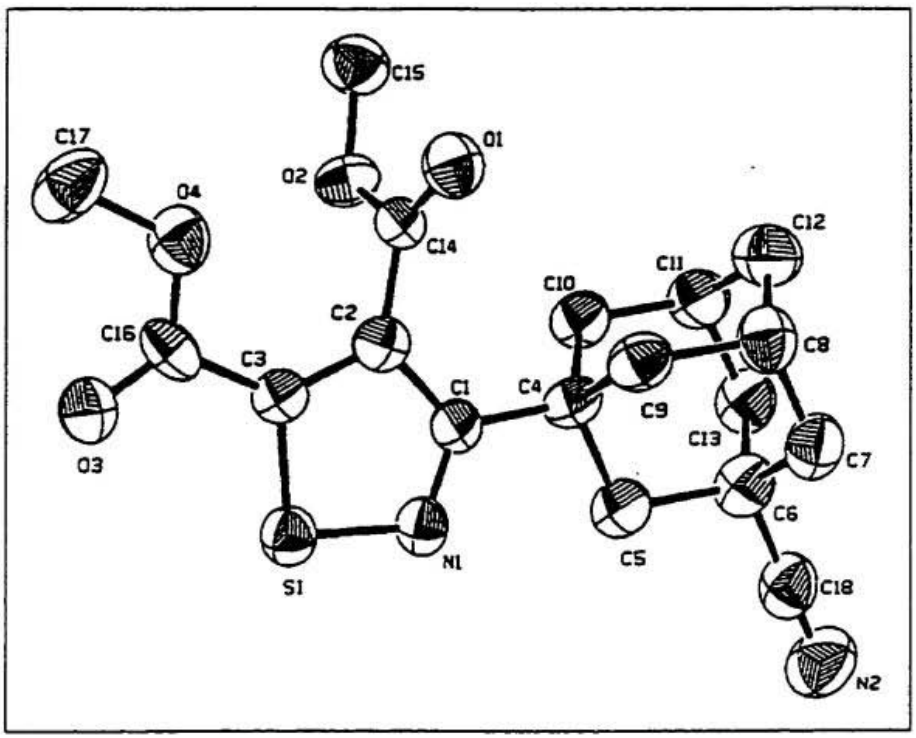


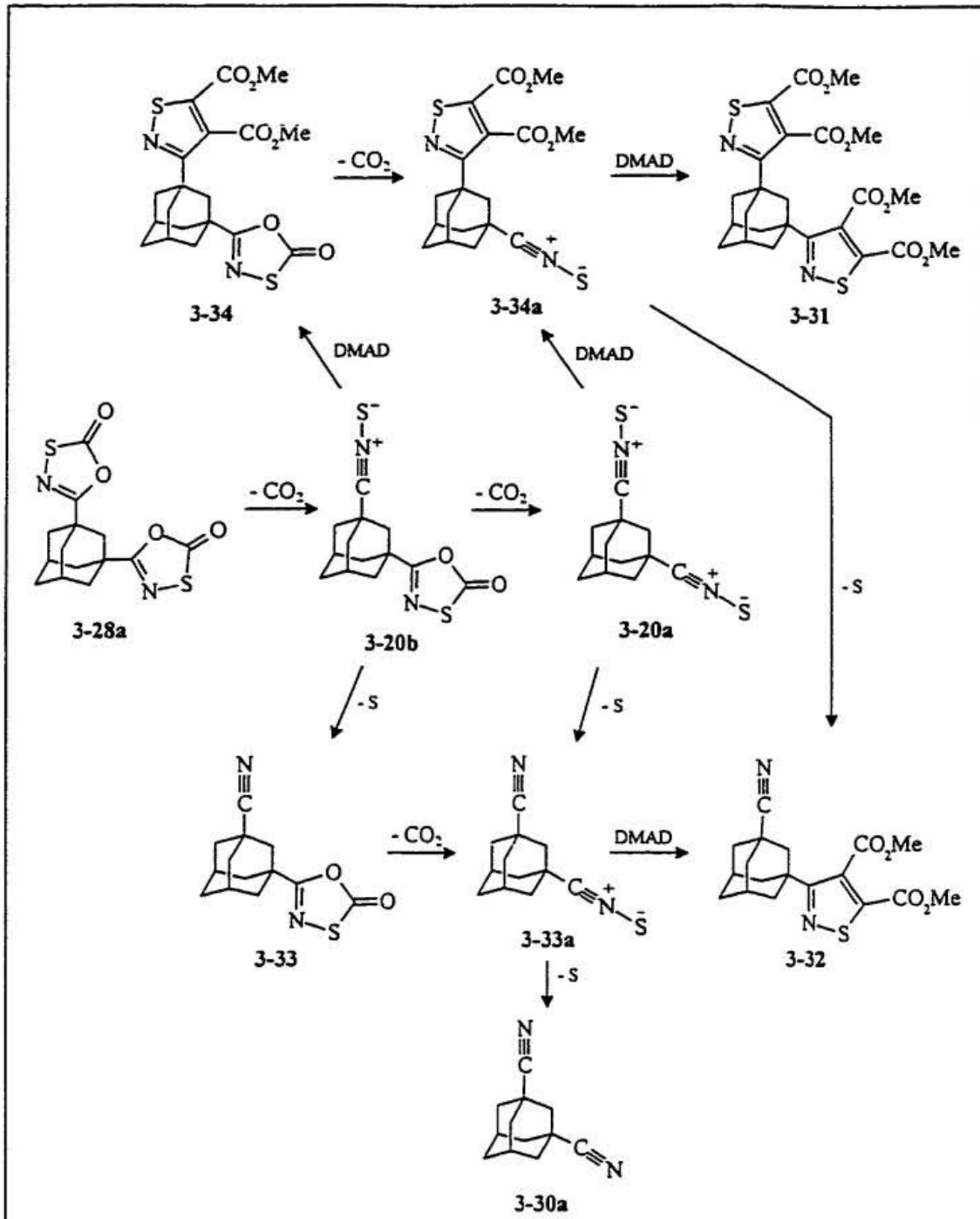
Figure 3-14 ORTEP view of 1-cyano-3-(4',5'-bis(methoxylcarbonyl)-isothiazol-3'-yl)-adamantane **3-32**

(recrystallized from aqueous methanol). In this work, plate-shaped crystals were obtained from ethyl acetate. Attempts to solve the crystal structure of the dinitrile **3-30a** were not successful due to the poor quality of the crystals. The initial ball-and-stick structure obtained for the molecule **3-30a** is shown in Figure 3-12.

The reactions of malonamide **3-27c** and 1,4-benzenedicarbonamide **3-27d** with ClSC(O)Cl did not produce compounds consistent with the expected reactions. The amides did not noticeably dissolve in toluene even under reflux. The expected products, bis(oxathiazolone), mono(oxathiazolone) and dinitrile are usually soluble in hot toluene and the disappearance of the insoluble amide is an indication of the completion of the reaction. All the solids recovered from these two reactions were found to be the unreacted amides (IR and m.p.). The fact that no reaction occurred could be that the energy required to break the strong hydrogen bonding network in the amide can not be compensated by the energy gained from the reaction. These results suggest that an alternative starting material may be required to avoid the high energy compensation for breaking down the hydrogen bonding network.

3.3.3 Generation of Bis(nitrile sulphides)

The generation of nitrile sulphides from oxathiazolones or other precursors has been discussed in the previous Chapters (1.3.2 and 2.3.2). There has been no report on the generation of bis(nitrile sulphides) even though some precursors bis(oxathiazolones) have been claimed[101]. As has been discussed previously, even the bulky adamantyl group did not appreciably stabilize the nitrile sulphide (2.3.2). Therefore, isolation of the



Scheme 3-15. Reactions of 1,3-adamantyl bis(oxathiazolone) 3-28a

bis(nitrile sulphide) from the precursors 1,3-adamantane-bis(oxathiazolone) **3-28a** or 1,8-octane-bis(oxathiazolone) **3-28b** is highly improbable. Trapping reagents (electron deficient alkynes) are necessary during the generation of the bis(nitrile sulphides) or they would ultimately decompose to the dinitriles and sulphur.

In the presence of DMAD in refluxing chlorobenzene, 1,3-adamantane-bis(oxathiazolone) **3-28a** gave the 1,3-adamantane-bis(isothiazole) **3-31** in 12% yield, 1-cyano-adamantane-3-isothiazole **3-32** in 44% yield, and the dinitrile **3-30a** in 44% yield (Scheme 3-15). The result is consistent with the reactivity pattern which has been observed for the generation of the mono(nitrile sulphides) from the precursor oxathiazolones. The product 1-cyano-adamantane-3-isothiazole **3-32** is good evidence for the competition between cycloaddition and decomposition of the bis(nitrile sulphide). The reactivity of adamantane-bis(nitrile sulphide) is comparable to that of adamantane-nitrile sulphide based on the yield of the cycloadduct(s) and their reactivities towards nitriles. The reaction of the bis(oxathiazolone) **3-28a** with dinitrile **3-30a** in refluxing chlorobenzene gave the dinitrile **3-30a** as the only product which was recovered from the reaction (Appendix 3). This indicates that the decomposition of 1,3-adamantane-bis(nitrile sulphide) is favourable while its cycloaddition to the nitrile is impossible under these conditions as observed for mono(nitrile sulphide). No reaction was observed between the nitrile sulphide and the nitrile. It may be due to a large HOMO-LUMO energy gap (see Fig. 1-3) between 1,3-adamantane-bis(nitrile sulphide) **3-20a** and dinitrile **3-30a** which could not be overcome under these conditions. There might be a reaction between the

bis(oxathiazolone) **3-28a** or more specifically the bis(nitrile sulphide) **3-20a** with a dinitrile such as Cl_3CCN or $(EtO_2C)CN$ with a LUMO at a lower energy. The same conclusion could also be drawn from the reaction of the adamantyl nitrile sulphide **2-6** with adamantane nitrile (2.3.3).

As discussed in the previous Chapters, the only direct evidence of a nitrile sulphide is from UV spectroscopy[10]. The mass spectrum has been used to provide indirect evidence as well[105]. In the mass spectra of all the oxathiazolones and isothiazoles synthesized in this work, a peak corresponding to the expected nitrile sulphide was observed. The intensity of this peak was directly related to the nature of the substituent. Aromatic substituents usually stabilize the nitrile sulphide more than the saturated substituents so that the intensities of peaks assigned to the aromatic nitrile sulphides are higher than those of peaks assigned to the alkyl nitrile sulphides, for example, **2-5** (1%), **3-28a** (0.3%), **3-28b** (1%), **3-41** (2%), **3-42** (3%). Benzene nitrile sulphide (*m/z* 135) has been detected in most of the aromatic oxathiazolones and isothiazoles in higher intensities such as **3-39** (3%), **3-40** (3%), **3-41** (26%), **3-42** (2%), **3-43** (5%), **3-44** (6%), **3-45** (20%), **3-46** (12%), **3-47** (14%), and **3-48** (10%). It was impossible to detect a bis(nitrile sulphide) by mass spectrometry presumably because of the low stability of the mono(nitrile sulphide).

3.3.4 Preparation and Cycloaddition Reactions of Isothiazolyl Oxathiazolones

The starting materials for the precursors 5-(3'-phenyl-isothiazole-4'/5'-yl)-1,3,4-oxathiazol-2-one **3-41/3-42** are 3-phenyl-isothiazole-4/5-carbonamides **3-39/3-40** which

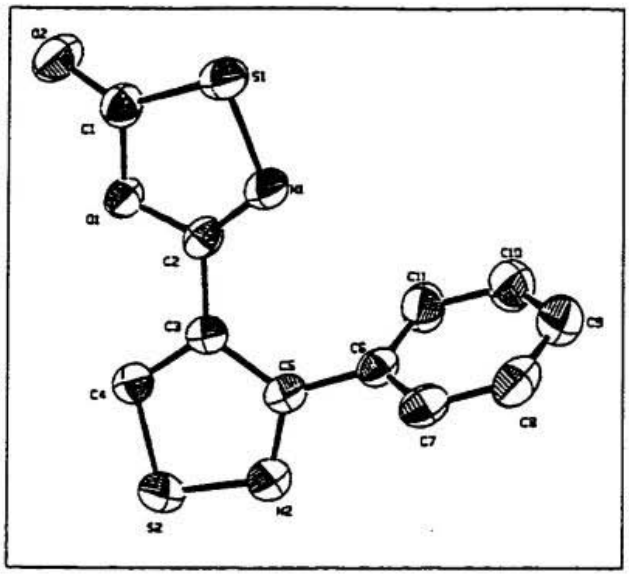


Figure 3-16 ORTEP view of 5-(3'-phenyl-isothiazol-4'-yl)-1,3,4-oxathiazol-2-one **3-41**

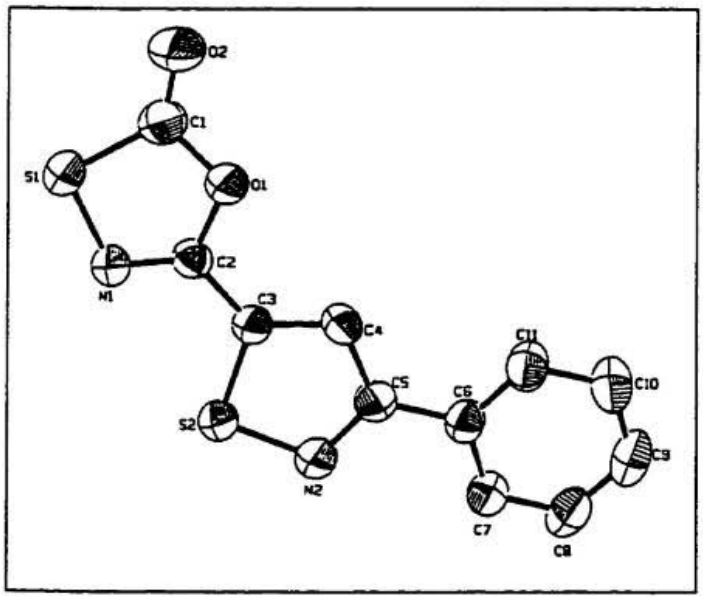
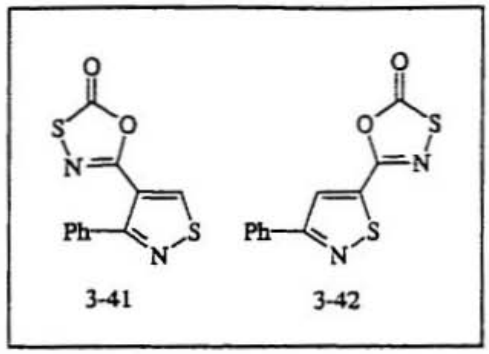


Figure 3-17 ORTEP view of 5-(3'-phenyl-isothiazol-5'-yl)-1,3,4-oxathiazol-2-one **3-42**

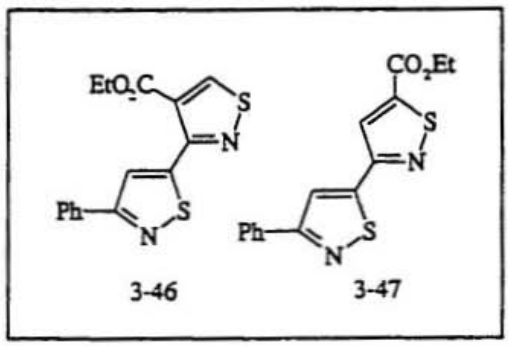
were made from the known compounds ethyl 3-phenyl-isothiazole-4/5-carboxylate **3-35/3-36**[14]. The intermediates 3-phenyl-isothiazole-4/5-carbonyl chloride **3-37/3-38** were not identified by spectroscopic methods and used without further purification. The amides **3-39/3-40** were identified by spectroscopic methods. The reactions of the amides with ClSC(O)Cl were carried out under the same general conditions as for the previously reported oxathiazolones and the yields of the corresponding oxathiazolones **3-41/3-42** are comparable to those of 5-aryl-1,3,4-oxathiazol-2-ones (Table 2-1). The oxathiazolones **3-41/3-42** were all identified by UV, IR, ^{1}H and ^{13}C NMR, MS, and elemental analysis, and their solid state structures were obtained by X-ray crystallography (Figures 3-16 and 3-17).



3-41 3-42

The cycloaddition reactions between 5-(3'-phenyl-isothiazol-5'-yl)-1,3,4-oxathiazol-2-one **3-42** with ethyl propiolate or DMAD are quite similar to those between other oxathiazolones and the corresponding dipolarophiles. Three expected products were isolated from the reaction of **3-42** with ethyl propiolate: the two isomers of the cycloadducts ethyl 3-(3'-phenyl-isothiazol-5'-yl)-isothiazole-4-carboxylate **3-46** and ethyl 3-(3'-phenyl-isothiazol-5'-yl)-isothiazole-5-carboxylate **3-47** and one decomposed product 3-phenyl-5-cyano-isothiazole **3-48**. The yield (74%) of the cycloadducts is not as high as that (84%)[14] from the reaction of 5-phenyl-1,3,4-oxathiazol-2-one with ethyl propiolate

because the reaction temperature is higher in the former reaction. The reaction of **3-42** with ethyl propiolate was carried out at 180°C while that of 5-phenyl-1,3,4-oxathiazol-2-one with ethyl propiolate was at 150°C[14]. The temperatures at which significant decomposition actually occurred were found to be at 110°C, 120°C, and 160°C for the three oxathiazolone derivatives: adamantyl **2-30**, phenyl-1,3,4-oxathiazol-2-one, and **3-42** respectively. These results suggest that the aromatic rings can also stabilize the oxathiazolone heterocycle and that the three rings in compound **3-42** may conjugate to each other in solution. The combined yield of the cycloadducts is still much higher than that of the nitrile, the decomposed product (16%), which indicates that the cycloaddition of the nitrile sulphide generated from the reaction is more favourable than its decomposition since the nitrile sulphide is also stabilized by the conjugated phenyl and isothiazole rings. These products were fully characterized by spectroscopic methods and elemental analysis. The regiochemistry of the two cycloadducts (**3-46** and **3-47**) were also confirmed by X-ray crystallography (Figures 3-18 and 3-19). The reaction of the oxathiazolone **3-42** with DMAD is quite similar to that of the compound with ethyl propiolate. The cycloadduct 3-phenyl-5-(dimethyl-4',5'-isothiazoldicarboxylate-3'-yl)-isothiazole **3-49** was isolated in 78% yield.



3-46 3-47

On the other hand, the reaction of 5-(3'-phenyl-isothiazol-5'-yl)-1,3,4-oxathiazol-2-

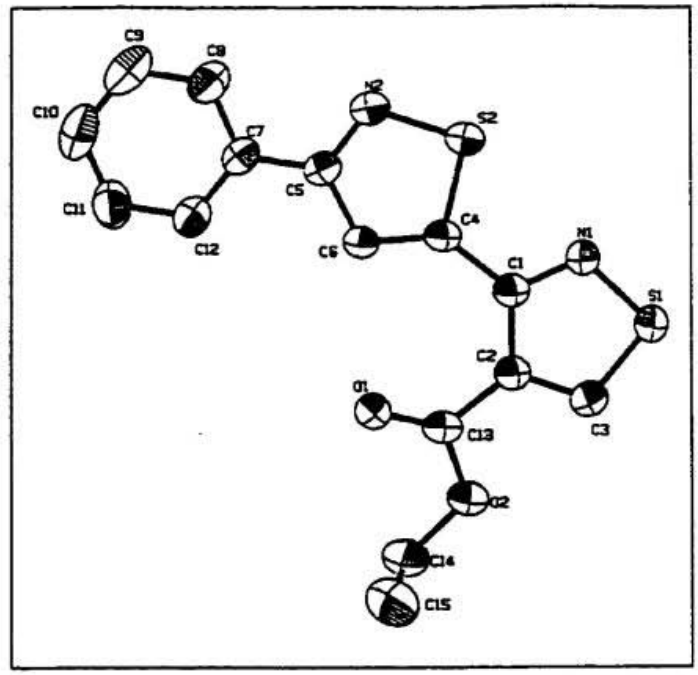


Figure 3-18 ORTEP view of ethyl 3-(3'-phenyl-isothiazol-5'-yl)-isothiazole-4-carboxylate **3-46**

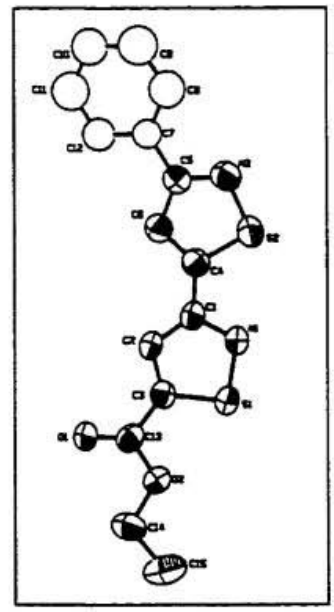


Figure 3-19 ORTEP view of ethyl 3-(3'-phenyl-isothiazol-5'-yl)-isothiazole-5-carboxylate **3-47**

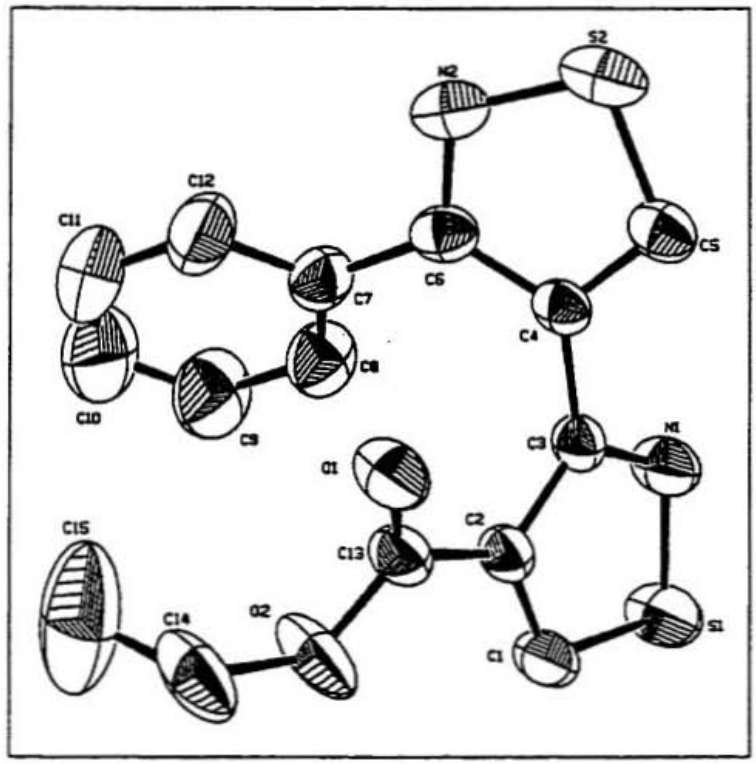
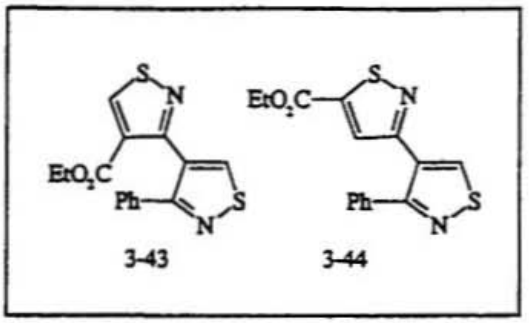


Figure 3-20 ORTEP view of ethyl 3-(3'-phenyl-isothiazol-4'-yl)-isothiazole-4-carboxylate **3-43**

one **3-41** with ethyl propiolate is different from the equivalent two reactions of its isomer **3-42**. The decomposition product nitrile was isolated in ~55% yield while the total yield of the cycloadducts was only ~45%. This result may indicate that a strong steric effect either destabilized the nitrile sulphide generated from the reaction or prevented the dipolarophile from attacking the nitrile sulphide. The other interesting result is the yield distribution of the two isomeric cycloadducts: 32% for **3-43** and less than 14% for **3-44**. Although the pure crystalline form of compound **3-44** could not be obtained, the structure of compound **3-43** was identified by X-ray crystallography (Figure 3-20). Steric effects could not fully explain why the yield of the apparently more sterically hindered isomer was higher than that of the sterically less hindered one. There is an intra-molecular hydrogen bond ($d_{O\text{-}H}$ = 2.166Å, ΣvdW = 2.70Å) between the hydrogen on the middle isothiazole ring and the carbonyl oxygen in the solid state structure of compound **3-43**[103]. It may suggest that some forces such as hydrogen bonding may induce the two reactants (the nitrile sulphide and the alkyne) to adopt their structures to approach to each other during the cycloaddition reaction.



3-43 3-44

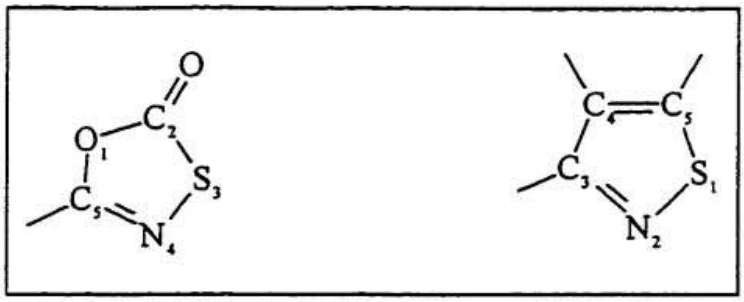
3.3.5 Structural Features of Oxathiazolones and Isothiazoles

The spectroscopic data (except NMR) for the known oxathiazolones and isothiazoles related to the 1,3-dipolar cycloaddition reactions of nitrile sulphides has not

been well documented. There had been no report of a solid state structure for any of these species until 1994[52]. The structures for some isothiazoles which were not prepared from the 1,3-cycloaddition reactions of the nitrile sulphides with dipolarophiles has been described before[75,106-108]. Table 3-1 and 3-2 summarize the bond distances and angles in the oxathiazolones and in the isothiazoles related to the nitrile sulphides (mostly from this work).

From Table 3-1, the distances of C-O bonds in the oxathiazolone rings are in the range of the standard C-O single bond distance or are slightly longer than the standard single bond. The C-S and S-N bond distances are slightly shorter than the corresponding standard single bonds. The table also clearly indicates that there is no electron delocalization in the heterocycles but there may be a limited conjugation between bonds (e.g. C_5=N_4-S_3-C_2) in the oxathiazolone. The limited conjugation may be consistent with the UV-visible spectra observed for these oxathiazolone derivatives. The UV-visible spectra of the oxathiazolones except those containing aromatic rings such as benzene (5-phenyl-1,3,5-oxathiazol-2-one) and isothiazole (**3-41, 3-42**) showed only one strong absorption at 214.0 ± 0.7 nm which is typical for the limited conjugated $\pi \rightarrow \pi^*$ transition as in the α,β-unsaturated ketones. Therefore the oxathiazolone heterocycle cannot be considered as aromatic.

On the other hand, all the bonds in the isothiazole rings (Table 3-2) are much shorter than their corresponding standard single bond distances, which is also true for the known isothiazoles reported previously[75,106-108]. This strongly suggests that there may be



Oxathiazolone Isothiazole

Table 3-1 Bond distance (Å) and angle (°) in oxathiazolones

compound	2-30	3-28a	3-28b	3-29a	3-41	3-42	literature
O_1-C_2	1.392	1.391 1.379	1.393	1.396	1.380	1.379	C-O 1.375 C=O 1.185
C_2-S_3	1.750	1.756 1.762	1.743	1.753	1.736	1.758	C-S 1.812 C=S 1.554
S_3-N_4	1.687	1.694 1.697	1.695	1.691	1.686	1.677	S-N 1.735
N_4-C_5	1.272	1.276 1.269	1.260	1.276	1.286	1.279	C-N 1.413 C=N 1.29
C_5-O_1	1.377	1.377	1.377	1.374	1.378	1.367	
S_3-N_4-C_5	106.9	109.1 109.5	109.5	109.4	108.4	109.4	
N_4-C_5-O_1	118.4	119.1	118.8	118.8	119.1	119.0	
C_5-O_1-C_2	112.0	111.5 112.4	111.7	111.9	111.1	111.2	
O_1-C_2-S_3	106.5	106.6	106.4	106.2	107.3	107.1	
C_2-S_3-N_4	93.5	93.6 93.2	93.6	93.8	94.1	93.1	
Ref.	52	102					75, 104

Table 3-2 Bond distance (Å) and angle (°) in isothiazoles

compound	2-32	3-31	3-32	3-41	3-42	3-43	3-46	3-47	literature
S_1-N_2	1.645	1.646	1.659	1.658	1.645	1.656	1.637	1.640	C-C 1.537
		1.650							C=C 1.335
N_2-C_3	1.323	1.315	1.281	1.322	1.327	1.321	1.328	1.338	C-S 1.812
		1.312				1.326	1.316	1.33	C=S 1.554
C_3-C_4	1.429	1.451	1.441	1.430	1.409	1.429	1.433	1.40	S-N 1.735
		1.419				1.430	1.422	1.41	
C_4-C_5	1.370	1.371	1.371	1.381	1.363	1.361	1.362	1.36	C-N 1.413
		1.365				1.362	1.354	1.37	C=N 1.29
C_5-S_1	1.690	1.716	1.692	1.687	1.712	1.684	1.679	1.713	
		1.709				1.692	1.711	1.704	
S_1-N_2-C_3	111.1	110.6	111.1	110.1	110.4	109.3	110.5	110.1	
		110.6				109.5	109.8	108.8	
N_2-C_3-C_4	114.0	115.2	116.0	114.6	114.8	115.2	114.5	115.1	
		114.8					114.9	115.7	
C_3-C_4-C_5	110.8	110.0	108.7	110.9	111.6	110.6	109.8	111.4	
		111.4				110.3	111.9	111.7	
C_4-C_5-S_1	109.5	109.1	110.4	108.8	108.6	109.4	110.4	109.2	
		108.4				109.5	107.9	107.6	
C_5-S_1-N_2	94.7	95.1	93.8	95.5	94.6	95.5	94.9	94.2	
		94.7				95.4	95.4	96.3	

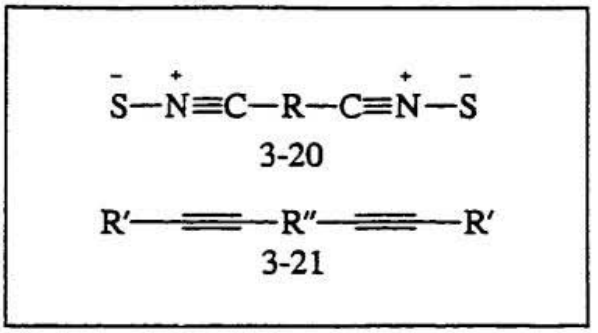
an electron delocalization in the isothiazole ring. This was supported by the UV-visible spectra of the isothiazoles. The UV-visible spectra of these isothiazoles showed three absorptions approximately at 197 nm, 230 nm and 278 nm which is typical for a conjugated 6π delocalized aromatic system. Thus, evidence from both the solid state structures and solution measurements supported the conclusion that the isothiazole rings prepared in this work must be five-membered-6π-electron heterocyclic aromatic systems since a lone pair on the sulphur atom must incorporate into the delocalized sextet of π electrons[109].

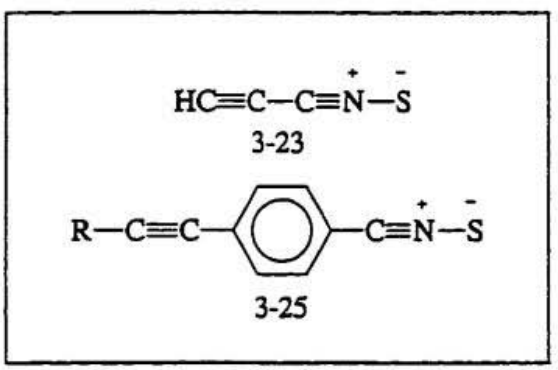
The solid state structure of compound **3-42** showed a relatively planar molecule (phenyl-isothiazolyl dihedral angle: 6.9°) while the phenyl ring of **3-41** has rotated 61° out of the plane of the isothiazole ring. Such a rotation should substantially diminish conjugation between the phenyl and isothiazole rings in compound **3-41**. Evidence that a similar structure is adopted in solution comes from its UV-visible spectrum, in which only one strong absorption at ~200 nm and a broad absorption (medium strong) at the range of 220-300 nm were observed. These can be explained as the result of the mixture absorptions of the two non-conjugated aromatic rings (Appendix 4 and 5). The C-C bonds (C_5-C_6) linking the phenyl and isothiazole rings in both molecules, however, are all between the C-C single bond and double bond in length and are not significantly different in length (1.473 Å in **3-41** and 1.482 Å in **3-42**).

3.3.6 Polyisothiazoles

As discussed in the introduction (3.1) and illustrated in Scheme 3-1,

polyisothiazoles might be prepared by using well designed starting materials such as bis(nitrile sulphides) (**3-20**, R = alkenes or alkynes or aryl) with bis(alkynes) (**3-21**, R" = alkenes or alkynes or aryl; R' = electron withdrawing groups) or acetylenyl nitrile sulphide (**3-23**) or alkynyl nitrile sulphides (**3-25**, R = electron withdrawing groups). In order to have highly reactive nitrile sulphides and alkynes for the reactions proposed in Scheme 3-1 and to synthesize the conjugated poly(isothiazoles), specific requirements for these substituents (R, R', and R") are necessary. For example, R in **3-25** and R' in **3-21** should be electron withdrawing groups and R in **3-20** and R" in **3-21** should be conjugated π systems. For the reactions concerning the bis(nitrile sulphides) (**3-20**), the preparations of specific precursors are essential. One type of the precursor, the bis(oxathiazolones), has been investigated. It is clear that not all the bis(oxathiazolones) can be prepared from the reaction of the corresponding bis(amides) with ClSC(O)Cl. The two examples are given in this work are malonamide and 1,4-benzenedicarbonamide which do not react with ClSC(O)Cl. Although oxalamide and other alkene and alkyne dicarbonamides (**3-27**) have not been examined,





it is most likely that they will not react with ClSC(O)Cl due to the strong hydrogen bonding network present in the bis(amides). Any electron withdrawing groups replacing the hydrogen in compound **3-23** would help the intermolecular 1,3-dipolar cycloaddition reaction. Compound **3-25** appears to be the best choice to conjugated poly(isothiazoles) because it should be much easier to make the highly reactive monomer and to control its side reactions such as polymerization of the alkyne group. In addition, the poly(heteroarylenes) **3-26** promise to be good candidates for possible new materials.

3.3.7 Conclusions and Future Work

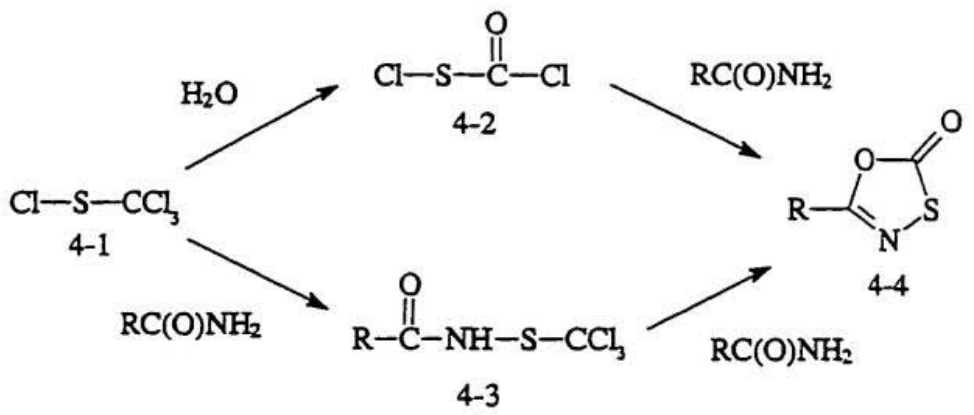
Two bis(oxathiazolones), compounds **3-28a** and **3-28b**, were prepared through similar reactions (Scheme 3-2). Upon heating, compound **3-28a** generated an intermediate, **3-20a**, which gave cycloadducts, mono(isothiazole) **3-32** and bis(isothiazole) **3-31**, in the presence of dipolarophile DMAD. Two phenyl-isothiazolyl-oxathiazolone isomers, **3-41** and **3-42**, were also prepared (Schemes 3-5 and 3-6). Further cycloaddition reactions of these two oxathiazolones with dipolarophiles (ethyl propiolate or DMAD) occurred and gave the cycloadducts, phenyl-isothiazolyl-isothiazoles (compounds **3-43**, **3-44**, **3-46**, **3-47** and **3-49**). The results from this work clarified that not all bis(oxathiazolones) can be synthesized from the reaction of an bis(amide) (**3-27**) with ClSC(O)Cl. From the results, it is also clear that highly conjugated isothiazolyl-oxathiazolones can be prepared and the corresponding nitrile sulphides will be generated at much higher temperatures (compared to less conjugated oxathiazolones). In order to synthesize conjugated poly(isothiazoles), it may require starting with some better designed nitrile sulphides such as **3-25** and **3-26**.

Chapter 4

A Novel Synthetic Route to 1,3,4-Oxathiazol-2-ones

4.1. Introduction

1,3,4-Oxathiazol-2-ones (**4-4**) were first synthesized as intermediates in the preparation of auxiliary products for the production of synthetic resins by Müllbauer and Weiss[101] in 1965. The oxathiazolones they prepared were also found to have fungicidal activities such as the inhibitory effect on mycelial growth of *Corticium rolfsii*. Although the direct preparation of the oxathiazolones was by the reaction of a carbonamide with chlorocarbonylsulphenyl chloride (**4-2**), an alternative two-step method could also be employed, which involved one more step, either in making chlorocarbonylsulphenyl chloride (**4-2**) by partial hydrolysis of perchloromethylmercaptan[101,110] or in forming the N-trichloromethylmercaptan carbonamide (**4-3**) from the reaction of a carbonamide with perchloromethylmercaptan (**4-1**) and then the closure of the oxathiazolone ring[111] (Scheme 4-1). The direct synthesis of 1,3,4-oxathiazol-2-ones is a better choice at laboratory scale



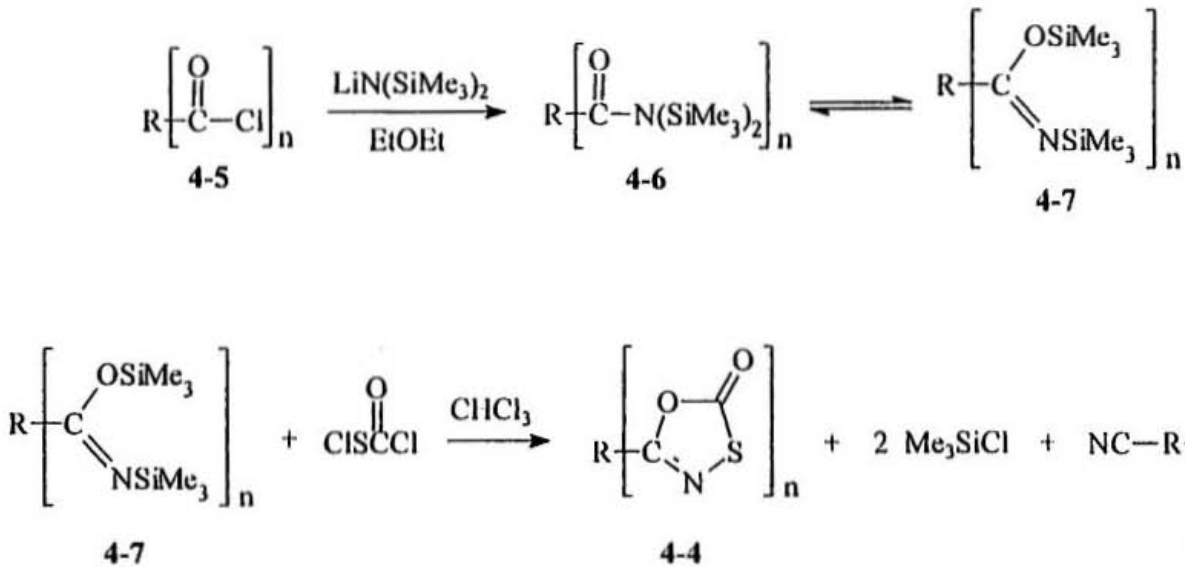
Scheme 4-1

because the amides and chlorocarbonylsulphenyl chloride are commercially available.

The chemistry and applications of 1,3,4-oxathiazol-2-ones had received little attention until the discovery[8] of the nitrile sulphides, a relatively new member of the 1,3-dipole family in 1970. As illustrated in Scheme 2-4, nitrile sulphides can react with dipolarophiles (unsaturated π-systems) to form heterocycles. Unlike other 1,3-dipoles, the nitrile sulphide group is very unstable and cannot be isolated under normal conditions so that suitable precursors are required for *in situ* generation of the nitrile sulphides. Among all the different precursors which are summarized in Table 2-1, 1,3,4-oxathiazol-2-one is still a better one. The oxathiazolone derivatives require relatively milder conditions to generate the nitrile sulphide and they are also readily prepared by using the reaction of organic carbonyl amides with chlorocarbonylsulphenyl chloride (Scheme 4-1). Many oxathiazolones have been prepared by using this method (Table 2-1). A problem, however, has been encountered in the syntheses of some oxathiazolone derivatives through this method as reported previously in this work. Even after many hours refluxing with ClSC(O)Cl, unreacted crotonamide ($MeCH{=}CHC(O)NH_2$)[36], malonamide ($H_2N(O)CCH_2C(O)NH_2$) (Chapter 3) and 1,4-benzenedicarbonamide (Chapter 3) were still recovered in 75%, 100% and 100% yield respectively. The strong hydrogen bonding network that exists in the amides might not be compensated by the cyclization reaction so that the reaction could be thermodynamically unfavourable (Chapter 3).

In order to prevent the hydrogen bonding network in the carbonyl amides, trimethylsilyl group (Me_3Si-) could be used to replace the hydrogen. In the reaction of

carbonyl amides with chlorocarbonylsulphenyl chloride, the by-product is HCl in addition to the product oxathiazolones. If the carbonyl amides are replaced by the *N,N*-bis(trimethylsilyl) carbonyl amides (**4-6**), in the reaction with chlorocarbonylsulphenyl chloride, the same product 1,3,4-oxathiazol-2-ones should be obtained. The secondary product in the reaction would be chlorotrimethylsilane instead of hydrogen chloride (Scheme 4-2). Chlorotrimethylsilane is volatile (b.p. 57°C) and can be easily removed. The new starting material, *N,N*-bis(trimethylsilyl) carbonyl amides (**4-6**) will be expected to have no strong hydrogen bonding and to be very soluble in any organic solvent. This is a strategic advantage because a soluble amide may react at much lower temperature as well. A disadvantage will be that the *N,N*-bis(trimethylsilyl) carbonyl amides (**4-6**), however, have to be handled under a moisture free atmosphere. Some bis(trimethylsilyl) carbonyl amides such as N,O-bis(trimethylsilyl) acetamide $MeC[=NSiMe_3]OSiMe_3$ and bis(trimethylsilyl) trifluoroacetamide $CF_3C[=NSiMe_3]OSiMe_3$ are commercially available. Other bis(trimethylsilyl) carbonyl amides (**4-6**) can be prepared from the reaction of the corresponding carbonyl chlorides (**4-5**) with lithium bis(trimethylsilyl)amide (Scheme 4-2).



a. n = 1, R = Me; b. n=1, R = CF_3; c. n = 1, R = *p*-$C_6H_5C_6H_4$;
d. n = 2, R = 1,4-C_6H_4; e. n =2, R = 4,4'-$C_6H_4C_6H_4$

Scheme 4-2. Preparation of oxathiazolones from bistrimethylsilyl carbonyl amides 4-6/7

4.2. Experimental

4.2.1. General Procedures

Reagents used in synthesis, 1,4-Cl(O)CC$_6$H$_4$C(O)Cl, MeC[OSiMe$_3$]=NSiMe$_3$, CF$_3$C[OSiMe$_3$]=NSiMe$_3$, ClSC(O)Cl, and ClS(O)Cl were purchased from Aldrich and used as received. Solvents were refluxed with the appropriate drying agent [CHCl$_3$ / P$_2$O$_5$, C$_6$H$_5$CH$_3$ / Na, EtOEt / CaH$_2$] and distilled under nitrogen prior to use.

4.2.2. Preparation of 5-Methyl-1,3,4-Oxathiazol-2-one, 4-4a

Chlorocarbonylsulfenyl chloride, ClSC(O)Cl, (3.4 g, 26 mmol) was added to a mixture of chloroform (48 mL) and *N,O*-bis(trimethylsilyl)acetamide (**4-7a**), CH$_3$C[OSiMe$_3$]=NSiMe$_3$, (2.5 g, 12 mmol) under nitrogen to give a clear and slightly yellow solution. The solution was heated at 59°C for 25 hours. The resulting dark red-brown solution was subjected to a distillation under vacuum (10^{-3} torr) at room temperature to remove the solvent, the by-product chlorotrimethylsilane and excess ClSC(O)Cl. The product 5-methyl-1,3,4-oxathiazol-2-one (**4-4a**) was then sublimed and trapped by a receiver submerged in an ice-water bath, 0.6 g (42%). IR (cm^{-1}): 1958 (w), 1913 (w), 1823 (s), 1761 (s), 1623 (s), 1430 (m), 1390 (m), 1259 (s), 1044 (m), 997 (m), 920(s), 785 (m), 652 (m). NMR, ^{1}H δ: 2.29 (s); ^{13}C δ: 173.9 (C=O), 158.4 (C$_{het}$), 16.1 (CH$_3$). MS [IE, 70eV] *m/z* (%): 117 (19, M$^+$), 89 (11, M - CO), 73 (23, CH$_3$-CNS), 60 (4, COS), 46 (29, NS), 43 (100, CH$_3$CO), 32 (20, S).

A CDCl$_3$ solution of *N,O*-bis(trimethylsilyl)acetamide and chlorocarbonylsulphenyl

chloride (molar ratio 1:2) was made under nitrogen. The reaction between the two compounds was monitored by ^{1}H NMR at 25°C. A spectrum was taken at time intervals of 20 min. The results (for a time period of 7 hr) were shown in the Appendix 6.

4.2.3. Attempted Preparation of 5-trifluoromethyl-1,3,4-Oxathiazol-2-one

Chlorocarbonylsulfenyl chloride, ClSC(O)Cl, (3.5 g, 27 mmol) was added to a mixture of chloroform (46 mL) and *N,O*-bis(trimethylsilyl)trifluoroacetamide **(4-7b)**, $CF_3C[OSiMe_3]{=}NSiMe_3$, (3.0 g, 12 mmol) under nitrogen to give a clear and slightly yellow solution. The solution was heated at 50°C for 24 hours. The reaction mixture did not leave any residue after removing the solvent by regular distillation.

Chlorocarbonylsulfenyl chloride, ClSC(O)Cl, (5.8 g, 44 mmol) was syringed into a mixture of toluene (85 mL) and *N,O*-bis(trimethylsilyl)trifluoroacetamide **(4-7b)**, $CF_3C[OSiMe_3]{=}NSiMe_3$, (5.7 g, 22 mmol) under argon to give a clear and slightly yellow solution. The solution was heated at 59°C for 4 hours. Dimethylacetylenedicarboxylate (DMAD) was then added into the mixture. The solution mixture was heated up to reflux for 18 hr. The volatile materials were removed from the reaction mixture under vacuum and the dark red liquid residue was passed through a column (silica gel: mesh 240 - 400, eluent $CHCl_3$). Only two fractions were recovered and none of them were found to be pure compounds (their ^{13}C NMR all showed three major peaks at 151.8, 74.3 and 53.2 ppm).

4.2.4. Preparation of 1,4-Bis[*N,O*-bis(trimethylsilyl)]benzamide

The diethyl ether (30 mL) solution of terephthaloyl chloride (5.0 g, 25 mmol) was

added dropwise into the yellow EtOEt (50 mL) suspension of lithium bis(trimethylsilyl)amide (8.3 g, 50 mmol) while stirring under argon. Upon completing the addition, the reaction mixture was refluxed overnight to give a yellow solution over a white solid (2.1 g, 100%) which was separated by gravity filtration. The yellow solution was subjected to a distillation under vacuum (10^{-3} torr) to remove the solvent and a yellowish solid (10.8 g, 97%) was obtained. This was identified as the expected product 1,4-bis[*N,O*-bis(trimethylsilyl)]benzamide (**4-7d**), NMR, ^{1}H δ: 7.54 (4H), 0.40-0.11 (36H); ^{13}C δ: 156.0 (C=N), 130.0 (C_{aro}), 127.8 (CH_{aro}), 1.22-0.37 (CH_3). MS [IE, 70eV] *m/z* (%): 452 (2, M^+), 451 (3, M-1), 450 (2, M-2), 436 (1, M - Me), 379 (2, M - $SiMe_3$), 378 (2, M - $HSiMe_3$), 365 (1, M - $NSiMe_3$), 362 (1, M - $HOSiMe_3$), 337 (8, M - $NSiMe_3$ and C_2H_4), 293 (8, $[Me_3Si]_2N(O)CC_6H_4$-CSiH), 265 (2, $[Me_3Si]_2N(O)CC_6H_5$), 264 (1, $[Me_3Si]_2N(O)CC_6H_4$), 263 (2, $[Me_3Si]_2N(O)CC_6H_3$), 147 (83, Me_3Si-$SiMe_3$+H or $Me_3SiOSiMe_2$), 75 (36, C_6H_3 or Me_3SiH_2), 73 (100, Me_3Si).

4.2.5. Preparation of 1,4-Bis(1',3',4'-oxathiazol-2'-one-5'-yl)benzene and 1-Cyano-4-(1',3',4'-oxathiazol-2'-one-5'-yl)benzene

1,4-Bis[*N,O*-bis(trimethylsilyl)]benzamide (**4-7d**) (5.0 g, 11 mmol) was dissolved in dry $CHCl_3$ (85 ml) to give a yellowish solution. Chlorocarbonylsulphenyl chloride (6.6 g, 50 mmol) was added into the solution under argon and heat was immediately evolved. The solution was refluxed for 24 hr while stirring under argon to give a yellow solution over a yellowish-white solid. Filtration of the reaction mixture gave a yellowish-white solid (1.2 g) and a yellow solution which gave a yellow solid (2.1 g) upon evaporation.

The yellowish-white solid turned pink in color upon exposure to light for several days and was identified as 1,4-bis(1',3',4'-oxathiazol-2'-one-5'-yl)benzene (**4-4d**) (39%), m.p. 198°C (dec.), IR (cm^{-1}): 1769 (m), 1736 (s), 1704 (m), 1602 (w), 1581 (w), 1406 (ms), 1314 (m), 1291 (m), 987 (m), 883(w), 856 (w), 721 (w), 684 (m); MS [IE, 70eV] *m/z* (%): 280 (30.19, M^+; [281 (4.18), 282 (3.22)]), 236 (3, M - CO_2), 206 (100, [COCONS]C_6H_4-CO; [207 (10.24), 208 (5.47)]), 178 (24, [COCONS]C_6H_4 or [OCNS]C_6H_4CO), 162 (10, OCC_6H_4CNS), 132 (64, OCC_6H_4CO), 130 (56, OCC_6H_4CN), 104 (45, C_6H_4CO), 102 (29, C_6H_4CN), 76 (33, C_6H_4); Anal. calcd.: C 48.39, H 1.63, N 11.29; found: C 36.78, H 1.82, N 8.47. The yellow solid from the solution was redissolved in $CHCl_3$ and passed through a column (silica gel 320-400 mesh) to give a white solid which was identified as 1-cyano-4-(1',3',4'-oxathiazol-2'-one-5'-yl)benzene (**4-8d**) (0.8 g, 36%), m.p. 167-168°C (dec. after melt), IR (cm^{-1}): 2233 (w), 1766 (m), 1730 (m), 1589 (w), 1551 (w), 1407 (ms), 1406 (ms), 1315 (m), 1290 (m), 1094 (m), 977 (m), 853 (w), 721 (m), 677 (w); NMR, ^1H δ: 8.11-8.09 (d, J = 7.1Hz, 2H), 7.79-7.82 (d, J = 7.1Hz, 2H); ^{13}C δ: 172.7 (C=O), 132.8 (C_{aro}), 130.1 (C_{aro}), 127.8 (C_{aro}), 117.6 (CH_{aro}), 116.0 (CN); MS [IE, 70eV] *m/z* (%): 204 (11, M^+), 177 (2, M - 27), 160 (4, NCC_6H_4-CNS), 149 (2, [OCNS]C_6H_3), 130 (100, NCC_6H_4CO), 102 (44, NCC_6H_4), 76 (10, C_6H_4); Anal. calcd.: C 52.94, H 1.98, N 13.73; found: C 51.68, H 2.18, N 12.87.

4.2.6. Preparation of 5-(4'-Biphenyl)-1,3,4-oxathiazol-2-one

4-Biphenyl-*N,O*-bis(trimethylsilyl)carbonamide **4-7c** (3.4 g, 9.9 mmol) [prepared by Neil Squires[112] from the reaction of the corresponding chloride **4-5c** with lithium

bis(trimethylsilyl)amide] was dissolved in 70 mL $CHCl_3$ to give a clear yellow solution. Chlorocarbonylsulphenyl chloride (2.8 g, 21 mmol) was then added into the solution and the reaction mixture was refluxed for 2 hr and stirred at room temperature for 20 hr. The resulting dark red-orange solution was allowed to stand in a fumehood to remove the excess ClSC(O)Cl and the solvent and an orange-yellow solid (2.8 g) was obtained. The solid was redissolved in $CHCl_3$ and loaded on a column (silica gel, 240-400 mesh) and eluted by a solvent mixture of toluene and hexanes (2:1). The desired product 5-(4'-biphenyl)-1,3,4-oxathiazol-2-one **4-4c** was obtained from the column and recrystallized from toluene as colorless plate-shaped crystals (1.5 g, 59%), m.p. 134.5-135.5°C, IR (cm^{-1}): 1778 (m), 1731 (s), 1703 (s), 1602 (ms), 1576 (m), 1554 (m), 1519 (m), 1406 (m), 1304 (ms), 1096 (m), 989 (m), 889 (m), 849 (m), 771 (m), 727 (s), 697 (m), 677 (m); NMR, ^1H δ: 8.04-8.01 (d, J = 7.1Hz, 2H), 7.72-7.69 (d, J = 7.1Hz, 2H), 7.63-7.61 (d, J = 7.1Hz, 2H), 7.50-7.40 (m, 3H); ^{13}C δ: 173.8 (C=O), 157.2 (C=N), 145.3 (C_{aro}), 139.4 (C_{aro}), 129.0 (C_{aro}), 128.4 (C_{aro}), 127.8 (CH_{aro}), 127.6 (C_{aro}), 127.1 (C_{aro}), 124.4 (C_{aro}); MS [IE, 70eV] *m/z* (%): 255 (18, M^+), 211 (8, M - CO_2), 179 (100, $C_6H_5C_6H_4$-CN), 153 (16, $C_6H_5C_6H_4$); Anal. calcd.: C 65.87, H 3.56, N 5.49; found: C 65.85, H 3.69, N 5.60.

4-2-7. Preparation of 4,4'-Biphenyl-Bis[*N,O*-bis(trimethylsilyl)carbonamide]

The diethyl ether (50 mL) solution of 4,4'-biphenyldicarbonyl chloride (6.4 g, 23 mmol) was added dropwise into the yellow EtOEt (150 mL) solution of lithium bis(trimethylsilyl)amide (7.5 g, 44 mmol) while stirring under argon. Upon completing the addition, the reaction mixture was refluxed for 20.5 hr. to give a yellow solution over

a white solid which was separated by regular filtration. The yellow solution was subjected to a distillation under vacuum (10^{-3}) to remove the solvent and a yellowish solid (10.5 g, 86.5%) was obtained and was identified as the expected product 4,4'-biphenyl-bis[*N,O*-bis(trimethylsilyl)]benzamide (**4-7e**), NMR, ^{1}H δ: 7.66 (d, J = 7.1Hz, 4H), 7.60 (d, J = 7.1Hz, 4H), 0.42-0.08 (m, 36H); ^{13}C δ: 156.0 (C=N), 141.8 (C_{aro}), 135.8 (C_{aro}), 130.7 (CH_{aro}), 128.9 (C_{aro}), 126.6 (C_{aro}), 1.31-0.40 (CH_3). MS [IE, 70eV] *m/z* (%): 528 (1, M^+), 527 (2, M-1), 526 (4, M-2), 455 (3, M - $SiMe_3$), 454 (2, M - $HSiMe_3$), 364 (3, M - $Me_3SiOSiMe_3$), 279 (4, $MeC_6H_4C(O)N(SiMe_3)_2$), 206 (5, $MeC_6H_4C(N)OSiMe_3$), 147 (89, Me_3Si-$SiMe_3$+H or $Me_3SiOSiMe_2$), 75 (59, C_6H_3 or Me_3SiH_2), 73 (100, Me_3Si).

4.2.7. Reaction of 4,4'-Biphenyl-Bis[*N,O*-bis(trimethylsilyl)carbonamide] with Chlorocarbonylsulphenyl Chloride

4,4'-Biphenyl-bis[*N,O*-bis(trimethylsilyl)carbonamide] **4-7e** (5.2 g, 9.8 mmol) was dissolved in $CHCl_3$ (100 mL) to give a clear yellow solution. Chlorocarbonylsulphenyl chloride (5.8 g. 44 mmol) was then added into the solution and the reaction mixture was refluxed for 9.5 hr and then stirred at room temperature for 11.5 hr. The resulting orange solution over an orange solid were separated by filtration. Both the solution and the solid (2.3 g, 66%) turned to yellow upon exposure to air. The solid was found to be insoluble in any solvent and started to decompose at 185°C without melting, IR (cm^{-1}): 1773 (s), 1734 (s), 1706 (s), 1598 (ms), 1547 (m), 1398 (m), 1303 (ms), 1177 (w), 1096 (m), 985 (ms), 884 (m), 829 (m), 721 (m), 681 (w); MS [IE, 70eV] *m/z* (%): 356 (2, M^+), 296 (1, M - COS), 280 (19, M - CO_2S), 236 (8, $NCC_6H_4C_6H_4CNS$), 206 (100, $NCC_6H_4C_6H_4CO$),

204 (73, $NCC_6H_4C_6H_4CN$), 177 (32, $NCC_6H_4C_6H_3$), 151 (36, C_6H_4-C_6H_3), 102 (6, CNSC(O)O). The product appeared to be 4,4'-biphenyl-[bis(1",3",4"-oxathiazol-2"-one)] **4-4e**.

The excess ClSC(O)Cl and the solvent were removed and an yellow solid (4.1 g) was obtained. The solid was significantly soluble in $CHCl_3$ and CH_2Cl_2 and sparingly soluble in acetone, toluene and diethyl ether and insoluble in hexanes. The solid was redissolved in $CHCl_3$. The resulting solution was passed through a column (silica gel, 240-400 mesh) and eluted by chloroform to give one of the desired products 5-[4'-(*p*-cyanophenyl)-phenyl]-1,3,4-oxathiazol-2-one **4-8e** (0.5 g, 18%), m.p. 177-179°C (dec.), IR (cm^{-1}): 2226 (w), 1773 (ms), 1597 (m), 1554 (w), 1304 (m), 1096 (m), 988 (m), 889 (m), 822 (m), 721 (m), 682 (w); NMR, ^1H δ: 8.10-8.07 (d), 7.80-7.71 (m); ^{13}C δ: 173.6 (C=O), 156.8 (C=N), 143.9 (C_{aro}), 143.1 (C_{aro}), 132.8 (C_{aro}), 130.2 (C_{aro}), 128.1 (C_{aro}), 127.8 (CH_{aro}), 125.7 (C_{aro}), 118.5 (C_{aro}), 112.1 (CN); MS [IE, 70eV] *m/z* (%): 280 (26, M^+), 236 (10, M - CO_2), 206 (100, $NCC_6H_4C_6H_4$-CO), 204 (57, $NCC_6H_4C_6H_4CN$), 177 (29, $NCC_6H_4C_6H_3$), 151 (42, $C_6H_4C_6H_3$), 102 (6, COC(O)SN); Anal. calcd.: C 64.28, H 2.88, N 10.00; found: C 62.85, H 2.95, N 9.30.

4.3. Results and Discussion

4.3.1. Preparation of N,N-bis(trimethylsilyl)carbonamide

Bis(trimethylsilyl)acetamide was the first bis(trimethylsilyl)carbonamide to be examined and it was prepared from the reaction of acetamide with excess trimethylchlorosilane in the presence of triethylamine as described by Birkofer and coworkers[113] in 1963. Most primary amides[114,115,116] (even some secondary amides) were readily silylated by use of this method to form bis(trimethylsilyl)carbonamides. Other alternative methods involved the reaction of metal (Na[117,118] and Li[119]) salts of bis(trimethylsilyl)amide with organic carbonyl chlorides or esters[117]. In Birkofer's method, the amides were usually insoluble in the solvent (benzene in most cases) so that the reactions were heterogeneous. Triethylamine was typically present for the purpose of absorbing the HCl generated from the reaction and to give triethylamine hydrochloride as an insoluble by-product. On the other hand, the reactions could be homogeneous when an appropriate solvent was used (diethyl ether, for example). The only by-product, a metal chloride (NaCl or LiCl), was insoluble in the solvent and could be removed by filtration.

The method used in this work was the reaction of lithium bis(trimethylsilyl)amide with the corresponding carbonyl chloride. It has been found that it is much easier to control these exothermic reactions by gradually adding one reactant into the other than quanitatively mixing them. The by-product LiCl was simply removed by filtration and

the product bis(trimethylsilyl)carbonamide **4-6** was obtained when the solvent and volatile material(s) were removed. Since the new disubstituted amides were moisture sensitive, only NMR and MS spectra were obtained. The amides were all used without further purification and their yields were based on the recovered masses of the crude products.

4.3.2. Structure of Bis(trimethylsilyl)carbonamide

Migration or rearrangement is a well known phenomenon for organic silicon compounds[114]. 1,2-, 1,3-, 1,4- and 1,5 migrations are all well studied and there are many different types of rearrangements/migrations such as, from carbon to carbon, carbon to oxygen, nitrogen to carbon, nitrogen to nitrogen, nitrogen to oxygen and nitrogen to sulphur. Therefore the actual structure of organic silicon compounds is always a question. 1,3-Migration of bis(trimethylsilyl)carbonamides (**4-6**) from N to O has been well studied[113-124]. ^{15}N and ^{1}H NMR investigations on bis(trimethylsilyl)carbonamides revealed that bis(trimethylsilyl)formamide (**4-6**, R = H) has the amide structure (**4-6**) while other bis(trimethylsilyl)carbonamides (R = CH_3, CF_3, C_2H_5, $CH(CH_3)_2$, $C(CH_3)_3$, C_6H_5, C_5H_4N, OCH_3, OC_2H_5) are in the imidate form (**4-7**)[115,118,123].

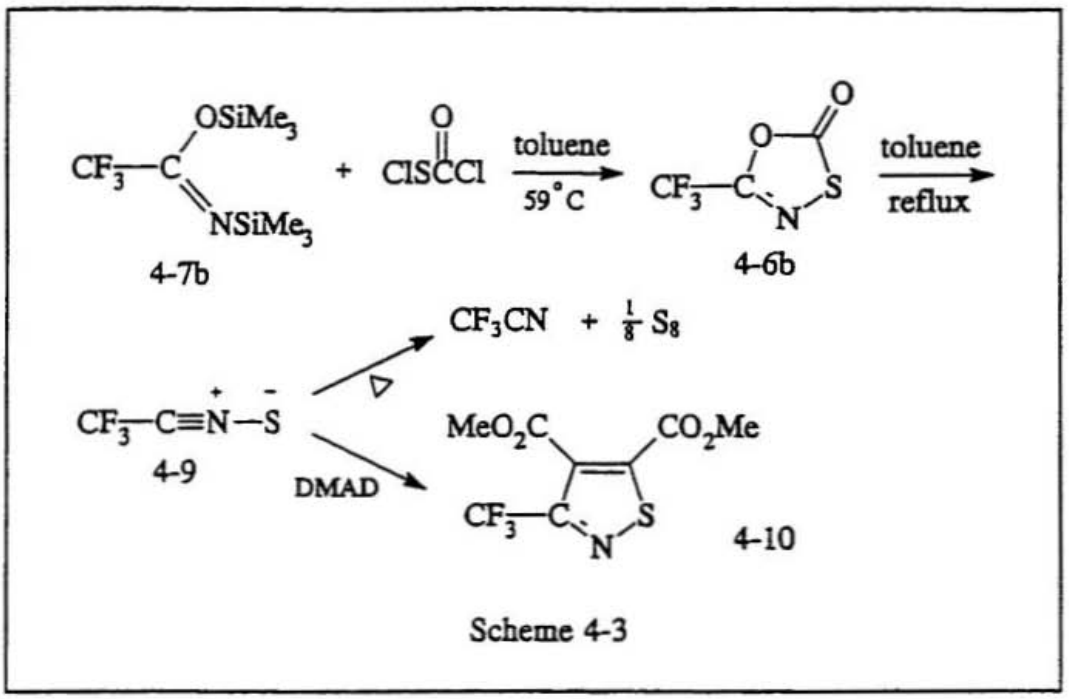
Two bis(trimethylsilyl)carbonamides were prepared in this work, **4-6d** and **4-6e**. The NMR and MS spectra for both compounds are very similar. The ^{1}H NMR showed two strong singlets in the region of $SiMe_3$ groups, 0.28 ppm and 0.11 ppm (**4-7d**), 0.31 ppm and 0.16 ppm (**4-7e**), strongly suggesting two different trimethylsilyl groups in the molecule. The ^{13}C NMR spectra of the two compounds revealed similar information: two strong peaks at the region of known $SiMe_3$ groups (1.23 ppm and 0.37 ppm for **4-7d**, 1.31

ppm and 0.40 ppm for **4-7e**). The mass spectra of both compounds had the cations of (M - Me_3Si-O-$SiMe_3$) and Me_3Si-O=$SiMe_2$ (*m/z* 147) which was the second strongest peak in intensity in both compounds. These results are very consistent with the imidate structure (**4-7**) of the amides. It is still not very clear that the two $SiMe_3$ groups in the imidate structure of the bis(trimethylsilyl)carbonamides are *cis-* or *trans-* to each other because of the high free energy of activation for the intramolecular exchange of trimethylsilyl groups in these amides[115]. A crystal structure of the bis(trimethylsilyl)carbonamide would answer this question. Attempts to obtain single crystals of compounds **4-7d** and **4-7e** in diethyl ether and pentane under nitrogen atmosphere were unfortunately not successful.

4.3.3. Preparation of Oxathiazolones

There is only one known way to prepare 5-substituted-1,3,4-oxathiazol-2-ones (**4-4**) and the starting materials are carbonyl amides ($RC(O)NH_2$) and either ClSC(O)Cl or perchloromethylmercaptan (**4-1**), the precursor to ClSC(O)Cl. The reaction of the amides with ClSC(O)Cl has been carried out in toluene[14,52,101-103,110,111] at 90-100°C. The amides ($RC(O)NH_2$) are insoluble in the cold solvent but most of them are slightly soluble in the hot solvent so that even marginal reactions can be pushed forward by giving off hydrogen chloride. All the oxathiazolones prepared from these reactions are very soluble in hot toluene but some of them can partially precipitate out when the solutions cool down. The by-products are the nitrile ($RC{\equiv}N$) and sulphur which come from the incidental decomposition of the product oxathiazolones.

The reaction of the bis(trimethylsilyl)carbonamide (**4-7**) with chlorocarbonylsulphenyl chloride has not been reported before. The first reaction examined was that of *N,O*-bis(trimethylsilyl)acetamide with ClSC(O)Cl in hot toluene (90-100°C). Unfortunately, no product was isolated from the reaction mixture for two major reasons: the high reaction temperature and high boiling point of the solvent (b.p. 110°C). Chloroform (b.p. 60.9°C) was chosen to replace toluene so that the reaction could be carried out at a lower temperature and the solvent could be easily separated from the product [even with the liquid product 5-methyl-1,3,4-oxathiazol-2-one **4-4a** (b.p. 75-76°C / 30 torr[14])]. 5-Methyl-1,3,4-oxathiazol-2-one **4-4a** has been synthesized from the reaction of the amide ($RC(O)NH_2$) with ClSC(O)Cl previously[14,101]. The reaction of *N,O*-bis(trimethylsilyl)acetamide with ClSC(O)Cl in $CHCl_3$ was examined. The NMR results (Appendix 6) showed that the reaction was complete within 6.5 hr even at room temperature. The yield of the product **4-4a** is 42% (compared to 56% at best by the old method[14]) and has not been optimized. This might be improved by modifying the reaction conditions (for example, reducing the reaction time). The reaction of *N,O*-bis(trimethylsilyl)trifluoroacetamide with ClSC(O)Cl was also examined under the same condition but no residue was left after removing the volatile solvent and starting materials by distillation. The same reaction was carried out in toluene at 59°C for 4 hr. Dimethyl acetylenedicarboxylate (DMAD) was then added into the mixture and the solution was refluxed for another 18 hr. The reaction of *N,O*-bis(trimethylsilyl)trifluoroacetamide with ClSC(O)Cl was expected to give 5-trifluoromethyl-1,3,4-oxathiazol-2-one **4-4b** which



Scheme 4-3

would then generate an unstable intermediate trifluoromethyl nitrile sulphide **4-9** upon heating. The nitrile sulphide **4-9** was also expected to be trapped by the dipolarophile DMAD to form the isothiazole **4-10** (Scheme 4-3). Unfortunately, both new compounds **4-4b** and **4-9** were not obtained.

The reaction of 4-biphenyl-N,O-bis(trimethylsilyl)carbonamide **4-7c** with ClSC(O)Cl gave the expected product oxathiazolone **4-4c** in 59% yield. The product has been identified by all spectroscopic means and the crystal structure of this compound has also been obtained (Fig. 4-4). The yield of the product could be improved once the reaction conditions are optimized (for example, the reaction can be carried out at a lower temperature or if the by-product chlorotrimethylsilane (b.p. 57°C) can be removed during

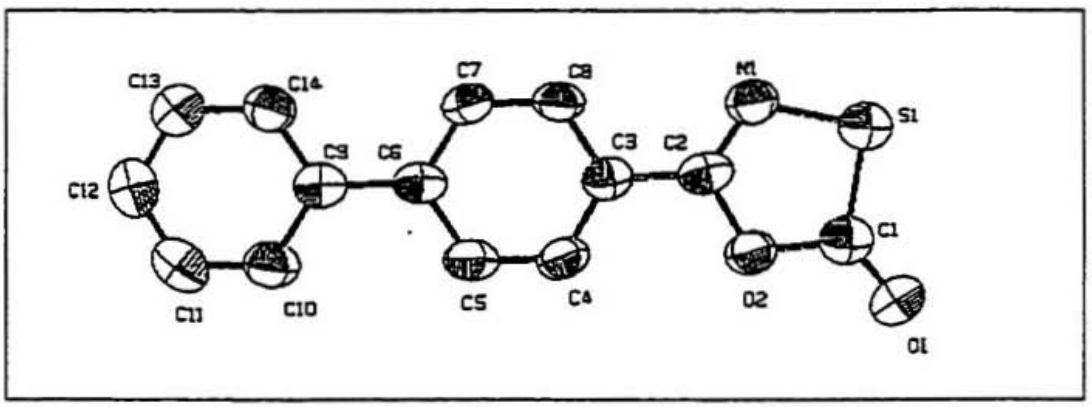


Figure 4-4 ORTEP view of 5-(4'-biphenyl)-1,3,4-oxathiazol-2-one **4-4c**

the reaction). The cycloadduct bis(oxathiazolones) (**4-4d**, **4-4e**) from the reactions of the bisamides (**4-7d** and **4-7e**) with ClSC(O)Cl could not be fully characterised because of their insolubility in any solvent which led the difficulty in purifications. The IR and MS spectra of compounds **4-4d** and **4-4e** gave good evidence for the structure of oxathiazolones and the observation of decomposition at 185-200°C for these two compounds was also a good supporting evidence for the conjugated oxathiazolones (see 3.3.4). The cyano-oxathiazolones (**4-8d** and **4-8e**), however, from these reactions are fairly soluble in chloroform and have been well characterised spectroscopically.

Based on the results above, it was shown that the bis(trimethylsilyl)carbonamides **4-7** or **4-6** could replace the amides ($RC(O)NH_2$) to react with ClSC(O)Cl to form 5-substituted-1,3,4-oxathiazol-2-ones **4-4**. It was synthetically easier to use the bis(trimethylsilyl)carbonamides than to use the poly(amides) $\{R[C(O)NH_2]_n\}$ for this type of reaction to avoid difficulty such as hydrogen bonding and insolubility, or when a low temperature is required for the reaction. The success of the reaction of bis(trimethylsilyl)carbonamide with ClSC(O)Cl to produce oxathiazolones has also brought up the question of the mechanism of the reaction of the amides $RC(O)NH_2$ with ClSC(O)Cl. There has been, to my knowledge, no report on the mechanism of this reaction. Reconstruction has to be done during the reaction so that the C=O double bond and C-N single bond in the amide can be converted into the C-O single bond and C=N double bond in the oxathiazolone (see 3.3.5 and Table 3-1). There is, however, no need to reconstruct these bonds for the reactions of bis(trimethylsilyl)carbonamides with

ClSC(O)Cl because of the imidate structure of the amide. Is it possible that there might be hydrogen migration of amides ($RC(O)NH_2$) to form the imidol (RC(OH)=NH) form during the reaction? What is the order of the reaction steps, for example, hydrogen migration to form imidol then attacking by ClSC(O)Cl or ClSC(O)Cl attaching to the nitrogen of the amide then hydrogen migration to form imidol then ring closure? It seems more reasonable, based on the chemistry observed in this work, that ClSC(O)Cl became attached to the nitrogen of the amide first, and the hydrogen migration could then occur. More studies would need to be done in order to answer these questions.

4.3.4. Structure of 5-(4'-Biphenyl)-1,3,4-oxathiazol-2-one

Structural features of the oxathiazolones prepared from the reaction of the amides ($RC(O)NH_2$) with ClSC(O)Cl were discussed in the previous Chapter (3.3.5). 5-(4'-Biphenyl)-1,3,4-oxathiazol-2-one was one of the oxathiazolones prepared from the bis(trimethylsilyl)carbonamides and it was the only one which was fully characterized spectroscopically and crystallographically. The IR, ^{1}H and ^{13}C NMR, MS spectra were very similar to those of the oxathiazolones discussed in 3.3.5. The mass spectrum showed the nitrile sulphide fragment in a higher intensity (8%) than any of the known oxathiazolones (see 3.3.3). This is consistent with the conclusion reached previously (3.3.3) that conjugation can stabilize the nitrile sulphide. The nitrile sulphide fragment appeared in relatively high intensity in the mass spectra of other oxathiazolones made from bis(trimethylsilyl)carbonamides (**4-4d**: 3%, **4-8d**: 4%, **4-4e**: 8%, **4-8e**: 10%). The solid state structure of **4-4c** reveals that the molecule is essentially planar (the dihedral

angles between the oxathiazolone ring and the middle ring, the middle ring and the terminal benzene ring, and between the two terminal rings are 3.24°, 3.24°, 1.72° respectively). The bond distances between any two of the rings are about 1.461Å and 1.480Å which are between the C-C single bond (1.537Å) and C=C double bond (1.335Å) (see Table 3-2). This may indicate some degree of electron delocalization among the rings. There is, however, no electron delocalization in the oxathiazolone ring (Appendix 2) which is also consistent with other oxathiazolones (3.3.5). From these results and those from other oxathiazolones, it is reasonable to believe that all the rings in oxathiazolones **4-4d**, **4-4e**, **4-8d**, and **4-8e** should be coplanar and there should be an electron delocalization among the rings in these molecules in solid state.

4.3.5. Conclusions and Future Work

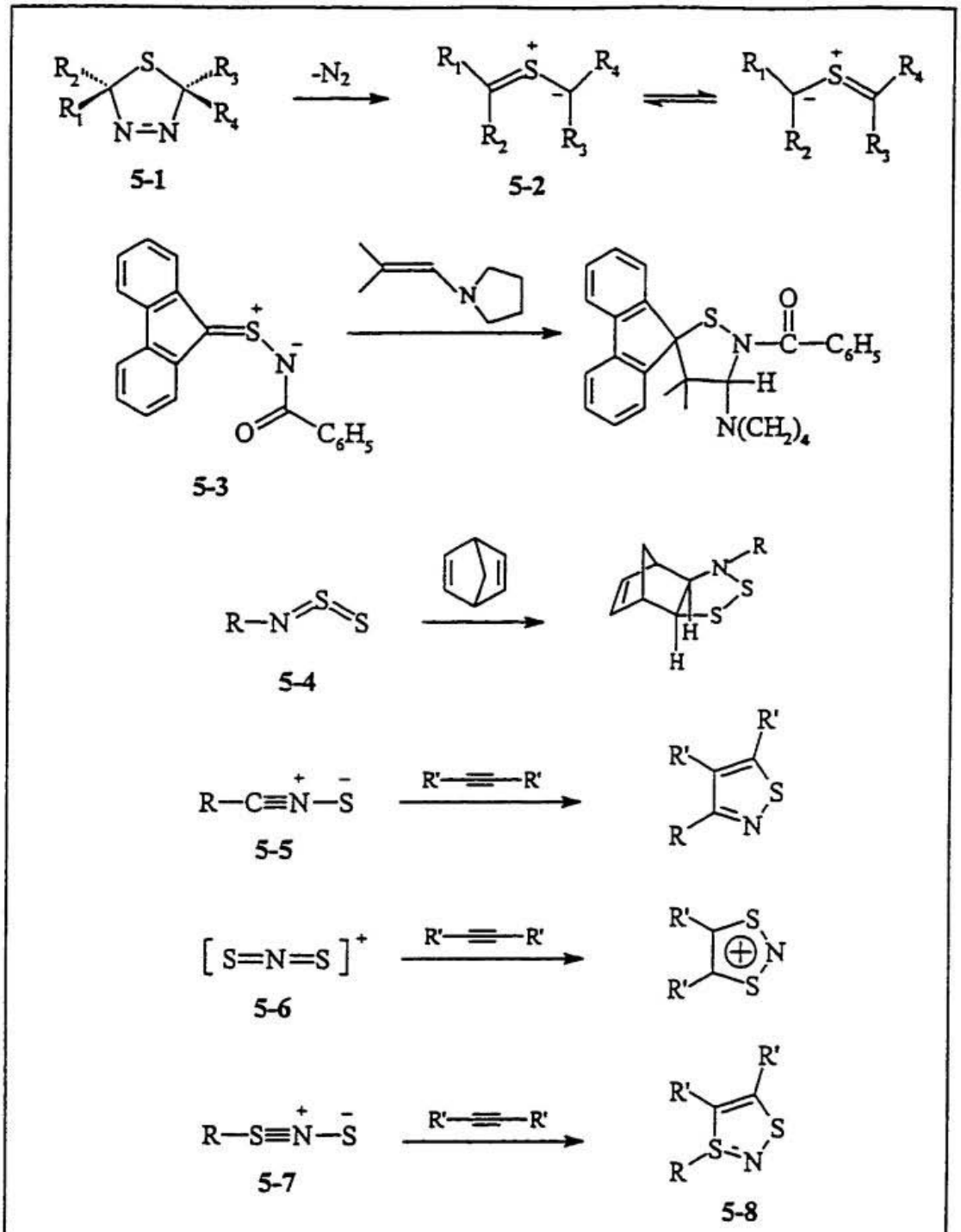
A novel synthesis of 5-substituted-1,3,4-oxathiazol-2-ones (**4-4**) from the reaction of bis(trimethylsilyl) carbonyl amides (**4-6** or **4-7**) with ClSC(O)Cl was discovered. This reaction was found to be a better route to 1,3,4-oxathiazol-2-ones than the old one because it was a homogeneous reaction and could take place at room temperature. Several oxathiazolones (compounds **4-4a**, **4-4c**, **4-4d**, **4-4e**, **4-8d** and **4-8e**) were synthesized from this reaction. More work such as optimizing the reaction conditions will need to be done for this reaction in the future.

Chapter 5

Attempted Generation of 1,3-Dipoles Containing Sulphur and Phosphorus

5.1. Introduction

The chemistry of 1,3-dipoles containing C, N, and O (examples are given in Table 1.1) has been well developed in the past century. These 1,3-dipoles have played a very important role in the syntheses of heterocyclic compounds,[1,125-130] natural products[131] and in chiral syntheses[132] of organic compounds. Much less is known about 1,3-dipoles containing heavier *p* block elements as the component atoms of the π manifold of 1,3-dipoles. Actually the "*Double Bond Rule*"[60,66] (it states that main group elements from the third period and below could not form π bonds with other elements or itself) excluded the possibility of π-bonding to heavier main group elements several decades ago. It is now possible to generate 1,3-dipoles and other species containing π bonds to the heavier *p* block elements since it has been proved that heavier nonmetal elements and even metal elements can form kinetically stable π bonds[66]. The first example of 1,3-dipoles containing heavier *p* block elements were the thiocarbonyl ylides (**5-2**)[133]. Thiocarbonyl ylides were very reactive intermediates which were generated from 1,3,4-thiadiazolines **5-1** by eliminating N_2 and were then trapped *in situ* by dipolarophiles (Scheme 5-1). Thiocarbonyl imine, fluorenethione *S*-benzoylimide **5-3**, was isolated and underwent 1,3-dipolar cycloaddition with *N*-isobutenylpyrrolidine[134] (Scheme 5-1) although its dipole structure was questioned[1]. Thiosulfinylamines[135] **5-4** were also isolated when an appropriate protective group such as 2,4-di(*tert*-butyl)-6-methyl-phenyl[136] was used. The 1,3-dipolar cycloaddition reaction of 2,4-di(*tert*-butyl)-6-methyl-phenyl-*N*-thiosulfinylaniline with norbornadiene took place even at room temperature[135]. All these

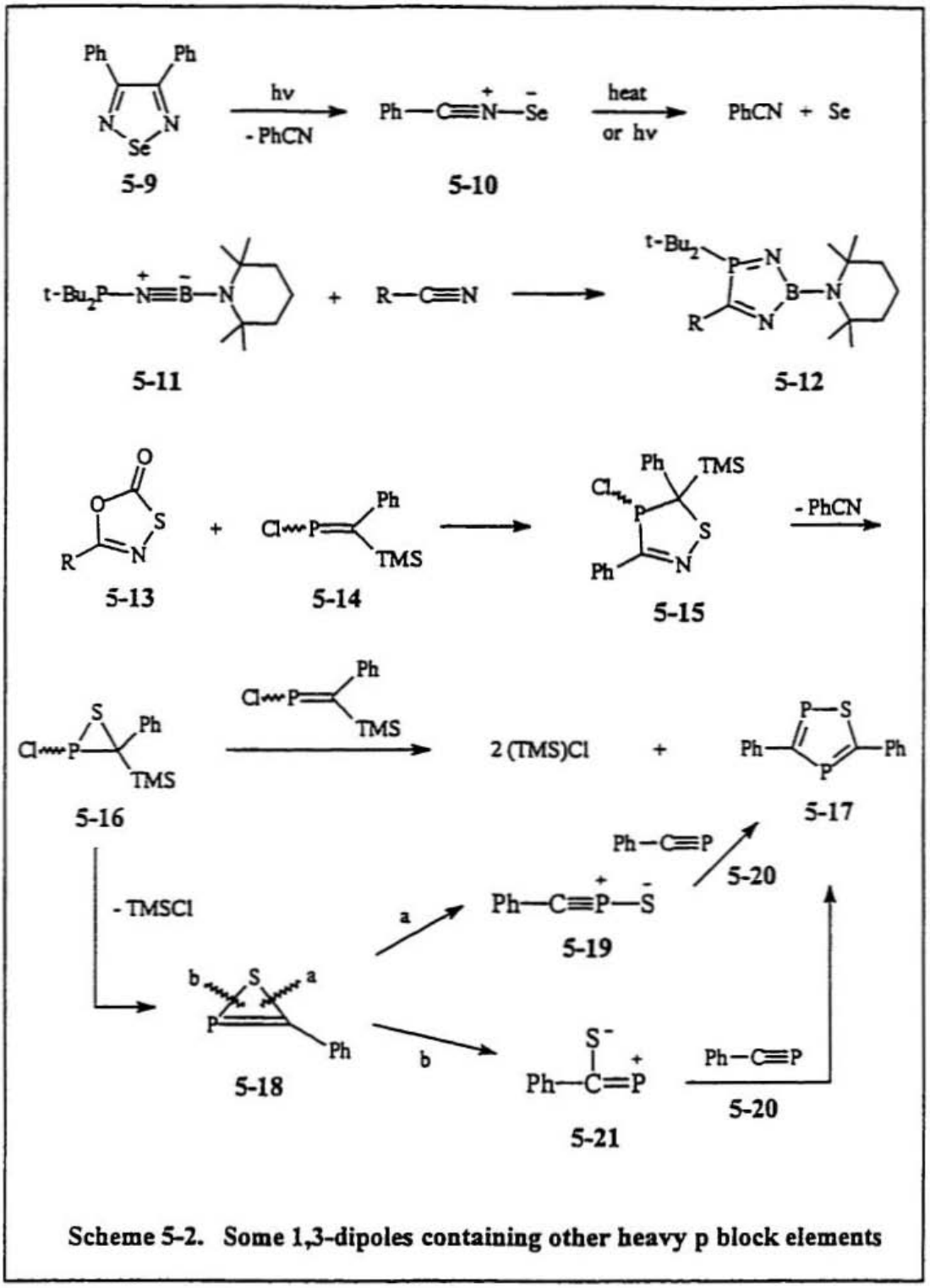


Scheme 5-1. Some 1,3-dipoles containing sulphur in π systems

species presented a fact that sulphur, one of the elements from the third period, was involved in the generation of new 1,3-dipoles. More and more efforts[7,137-138] have been made to generate new 1,3-dipoles incorporating sulphur as the component atoms. A recent example of this kind of 1,3-dipole is the very reactive intermediate nitrile sulphide[7] (**5-5**) which also contains a sulphur as one of the component atoms. The chemistry (mostly cycloaddition and decomposition reactions) of nitrile sulphides has been discussed in the previous chapters. An isolated inorganic species, the dithionitronium cation ([S=N=S]$^+$, a "pseudo-1,3-dipole"[137], **5-6**), can also undergo 1,3-cycloaddition reactions with alkynes and alkenes. Other similar compounds (non 1,3-dipole) such as the *N*-sulfinyl compounds[138] (R-N=S=O) and sulfodiimides[138] (R-N=S=N-R') were isolated in their stable forms but they reacted as dipolarophiles or dienophiles in the cycloaddition reactions. In the examples above, the sulphur atom can be in small reactive π systems only under circumstances that keep them from forming σ bonds. For example, they have to be trapped when they are generated from the precursors (for nitrile sulphides and thiocarbonyl ylides) or they have to be protected by bulky groups (for thiosulfinylamines). These examples strongly suggest that it may be possible to generate new 1,3-dipoles that contain a formally π bonded sulphur atom such as R-S≡N-S **5-7** (Scheme 5-1) when the appropriate technical protections, such as a bulky R group, a suitable precursor and a trap for the reactive intermediate, are applied.

Other heavier *p* block elements such as selenium and phosphorus have also been used for the generation of new 1,3-dipoles. 3,4-Diphenyl-1,2,5-selenadiazole (**5-9**) was

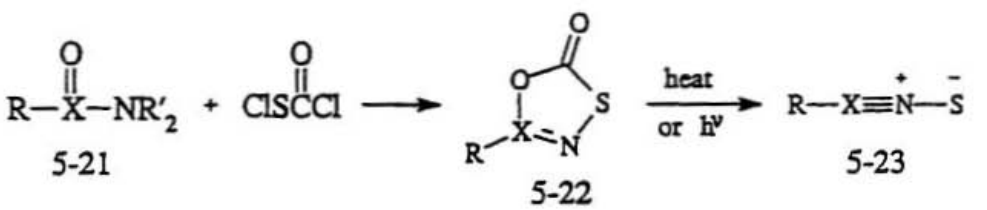
used to generate the nitrile selenides (Ph-C≡N-Se, **5-10**), the selenium analogues of nitrile oxides (R-C≡N-O) and nitrile sulphides (**5-5**). Although the attempted isolation of the nitrile selenides was not successful, a transient UV-vis spectrum with λ_{max} at *ca.* 255, 325, 360 and 390 nm during the UV photolysis of **5-9** at 20-85 K in PVC film was observed and was believed an evidence for the existence of the intermediate nitrile selenide[139]. (Di-*tert*-butylphosphanylimino)-2,2,6,6-tetramethylpiperidino)borane (**5-11**), a so called BNP 1,3-"dipole", can undergo [3+2] cycloaddition reactions with heteroallenes X=C=Y (X,Y = O, S, N) or nitriles to form five-membered heterocycles **5-12** (Scheme 5-2) while its nitrogen analogues prefer [2+2] cycloaddition reactions[140]. The first alleged 1,3-dipole containing phosphorus was reported by Märkl and Hölzl[141] in 1989. The reaction of the oxathiazolone **5-13** with a phosphaalkene **5-14** gave thiodiphosphole **5-17** as one of the products (Scheme 5-2). Further study revealed that the cycloadduct **5-15** could be obtained and then give the thiophosphirane **5-16** by eliminating a nitrile. The thiophosphirane reacted with phosphaalkene **5-14** or its decomposition phosphaalkyne **5-20** to form the final product thiodiphosphole **5-17**. Based on the result of the reaction and the fact that thiophosphirene **5-18** could be formed from thiophosphirane **5-16**[142], a mechanism was proposed in which a very reactive intermediate phosphaalkyne sulphide **5-19** was generated (through path *a*). A subsequent more careful examination[143] showed that the thiophosphirane could react with unsaturated systems such as alkynes to form five-membered heterocycles by eliminating TMSCl and then breaking the S-P bond (through path *b*) instead of the S-C bond for the cycloaddition. The phosphaalkyne



Scheme 5-2. Some 1,3-dipoles containing other heavy p block elements

sulphide **5-19**, a phosphorus derivative of the nitrile sulphides, was not generated from the reaction.

The work that will be reported in this chapter will describe our efforts to generate the first 1,3-dipoles **5-23** in which sulphur is used as the terminal component atom (to replace the carbon in the nitrile sulphides **5-5**) of the 1,3-dipoles or where phosphorus occupies the central position (to replace the nitrogen in the nitrile sulphides **5-5**) in the π manifold (Scheme 5-3). The target compounds will be very similar in structure and bonding to the known nitrile sulphides **5-5**, which are highly reactive and useful in synthetic reactions. The syntheses of these new 1,3-dipoles will require preparation of



Scheme 5-3

precursors **5-22** related to those known for the nitrile sulphides. These precursors are currently unknown and will need to be prepared for the first time (Scheme 5-3).

5.2. Experimental

5.2.1. General Procedures

Reagents used in synthesis, *p*-$CH_3C_6H_4SO_2Na{\cdot}xH_2O$, $LiN[Si(CH_3)_3]_2$, $C_6H_5SO_2NH_2$, *p*-$CH_3C_6H_4SO_2NH_2$, ClSC(O)Cl, and ClS(O)Cl were purchased from Aldrich and used as received. Solvents were refluxed with the appropriate drying agent [$CHCl_3$ / P_2O_5, $C_6H_5CH_3$ / Na, EtOEt / CaH_2] and distilled under nitrogen prior to use. ^{31}P NMR spectra were recorded on a General Electric 300 MHz instrument. Chemical shifts are reported in ppm (high frequency positive) relative to the standard (85% H_3PO_4).

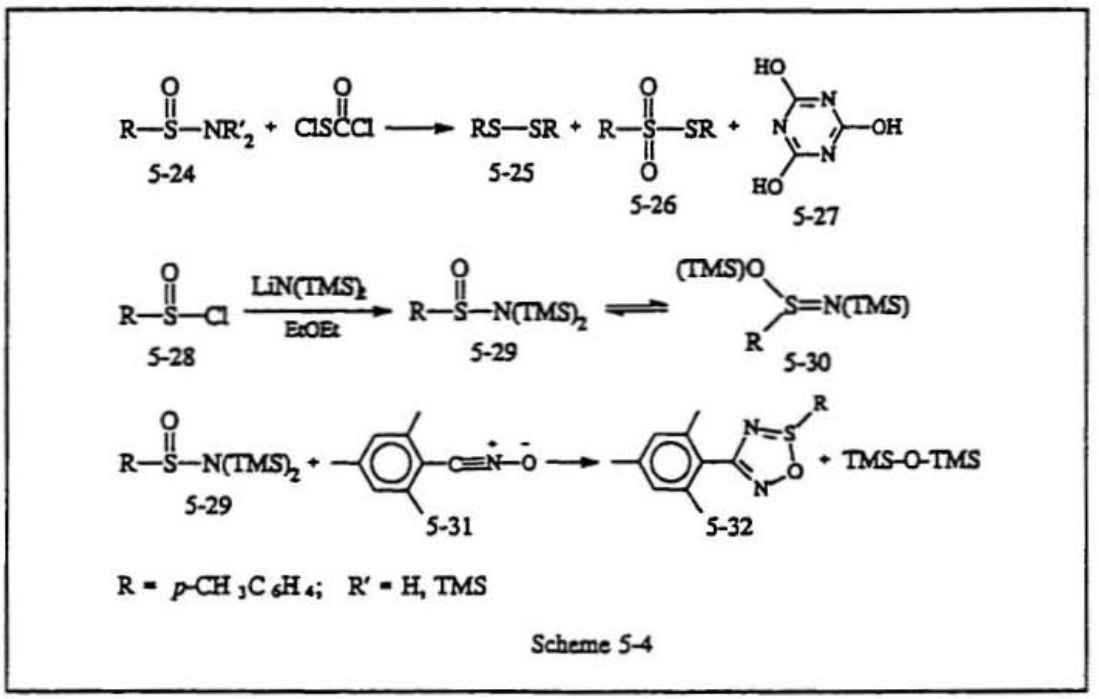
5.2.2. Preparation of *p*-Toluenesulfinamide

p-Toluenesulfinyl chloride (freshly prepared by following the standard procedure[144]), $CH_3C_6H_4S(O)Cl$ (48.3 g, 276 mmol), was mixed with dry diethyl ether (200 mL) under nitrogen to give a yellow solution. The solution was cooled down to -78°C (dry ice/acetone bath). Ammonia gas was then slowly bubbled through the solution with vigorous stirring at -78°C. A yellowish white solid (with some reddish color) immediately precipitated. Ammonia gas was continuously bubbled through the yellowish white slurry for 24 hr to give a white slurry. The mixture was extracted by dry diethyl ether (500 mL) and dry chloroform (500 mL). The combined extracts were then allowed to evaporate to dryness under vacuum to give a white solid which was identified as *p*-toluenesulfinamide **5-24** (R' = H) (19.2 g, 45%), m.p. 114-116°C (lit.[145] 117°C), Anal. calcd.: C 54.17, H 5.84, N 9.02; found: C 53.88, H 5.87, N 9.04.

5.2.3. Reaction of *p*-Toluenesulfinamide with ClSC(O)Cl

p-Toluenesulfinamide **5-24** (R' = H) (1.9 g, 12 mmol) was mixed with toluene (46 mL) to give a slightly pink solution over a white solid. Chlorocarbonylsulfenyl chloride, ClSC(O)Cl, (4.1 g, 31 mmol) was added to the mixture at room temperature under nitrogen to change the solution into a dark red-brown and the previously insoluble amide was observed to completely dissolve. The solution was refluxed for 18 hours to give a yellow solution over a white solid. The white solid was filtered out and identified as a known compound, cyanuric acid (1,3,5-triazine-2,4,6-(1H, 3H, 5H)-trione) **5-27** (0.3 g, 57%), m.p. >400°C, IR (cm^{-1}): 3147 (s), 3050 (s), 1764 (ms), 1721 (ms), 1409 (s); MS [IE, 70eV] *m/z* (%): 129 (100, M$^+$), 86 (16, M - HOCN), 43 (81, M - 2[HOCN]). The yellow solution was allowed to evaporate and a dark brown liquid was obtained. the liquid was diluted with $CHCl_3$ and passed through a column with $CHCl_3$. Three products were collected from the column: S_8, a white solid identified as *p*-toluenethiol-*p*-toluenesulfonate **5-26** (0.75 g, 22%), m.p. 72.5-73°C, IR (cm^{-1}): 3083-3033 (multi, m), 1591 (m), 1489 (m), 1448 (w), 1399 (w), 1378 (w), 1323 (s), 1292 (m), 1180 (m), 1139 (s), 1077 (m), 1017 (w), 806 (m), 703 (w), 652 (ms); NMR, ^1H δ: 7.46-7.43 (d, 2H), 7.24-7.12 (m, 6H), 2.42 (s, 3H), 2.37 (s, 3H); ^{13}C δ: 144.5 (C_{aro}), 142.0 (C_{aro}), 140.3 (C_{aro}), 136.4 (C_{aro}), 130.2 (CH_{aro}), 129.3 (C_{aro}), 127.5 (C_{aro}), 124.4 (C_{aro}), 21.6 (CH_3), 21.4 (CH_3); MS [IE, 70eV] *m/z* (%): 278 (20, M$^+$), 155 (22, $MeC_6H_4SO_2$), 139 (100, MeC_6H_4SO), 123 (41, MeC_6H_4S), 91 (82, MeC_6H_4); Anal. calcd.: C 60.40, H 5.07, N 0.00, S 23.03; found: C 59.99, H 5.01, N 0.18, S 20.79; and a reddish sticky solid which was

identified as *p*-toluenedisulfide **5-25** (1.5 g, 49%), m.p. 43-46°C, MS [IE, 70eV] *m/z* (%):



Scheme 5-4

246 (88, M^+), 213 (4, M - HS), 182 (11, $MeC_6H_4C_6H_4Me$), 123 (100, MeC_6H_4S), 91 (17, MeC_6H_4).

p-Toluenesulfinamide **5-24** (R' = H) (0.6 g, 3.8 mmol) was mixed with chloroform (30 mL) to give a cloudy solution at -23°C (dry ice/CCl_4 bath). Chlorocarbonylsulfenyl chloride (1.7 g, 13 mmol) was added dropwise into the mixture at the temperature under nitrogen and no change was observed. The mixture was stirred at the same temperature for 2 hr to give a cloudy yellow solution. The solution was then warmed to room temperature and stirred for another 17 hr. Only a yellowish-green, cloudy solution was obtained. After a filtration followed by evaporation under vacuum, the solution gave only

one compound (white solid) which was identified (m.p. and IR) as the unreacted amide.

5.2.4. Preparation of Bis(trimethylsilyl)-*p*-toluenesulfinamide

Lithium bis(trimethylsilyl)amide (35 g, 209 mmol) was mixed under nitrogen with dry diethyl ether (250 mL) to give a white suspension. *p*-Toluenesulfinyl chloride **5-28** was dissolved in dry diethyl ether (50 mL) and was added dropwise into the suspension at room temperature over an hour. The white suspension was then refluxed for 72 hr (under nitrogen). The fine white powder (LiCl) was filtered off from the reaction mixture to give a clear yellow solution. The solvent was pumped off and a white solid was obtained. The solid was dissolved in dry pentane and colorless crystals were obtained (47.3 g, 76%) upon slow removal of the solvent. The product was identified as *N,N*-bis(trimethylsilyl)-*p*-toluenesulfinamide **5-29**, NMR, ^{1}H δ: 7.42-7.40 (d, 2H), 7.21-7.20 (d, 2H), 2.34 (s, 3H), 0.219-0.169 (m, 18H); ^{13}C δ: 146.4 (C_{aro}), 139.8 (C_{aro}), 129.0 (C_{aro}), 125.8 (C_{aro}), 21.0 (CH_3), 2.83 ($SiCH_3$); MS [IE, 70eV] *m/z* (%): 299 (7, M^+), 284 (2, M - 15), 208 (17, $MeC_6H_4S{=}NSiMe_3$), 179 (16, $MeC_6H_4S{=}N{=}SiHMe$), 149 (31, $Me_3SiOSiHMe_2$ + H), 147 (43, $Me_3Si{-}O{=}SiMe_2$), 73 (100, Me_3Si).

^{1}H NMR spectra of *N,N*-bis(trimethylsilyl)-*p*-toluenesulfinamide **5-29** in $CDCl_3$ at different temperatures (-60°C - 60°C) under nitrogen were recorded and are given in Appendix 7.

5.2.5. Reaction of *N,N*-bis(trimethylsilyl)-*p*-toluenesulfinamide with ClSC(O)Cl

N,N-Bis(trimethylsilyl)-*p*-toluenesulfinamide (**5-24**, R' = TMS) (2.5 g, 8 mmol) was dissolved in 50 ml dry $CHCl_3$ at -50°C (dry ice / MeCN bath) and

chlorocarbonylsulphenyl chloride (3.5 g, 27 mmol) was added into the solution under nitrogen while the solution was stirring. The clear light yellow solution turned yellow then a deep dark green during the stirring at -50°C in 26 hr. and became dark purple-red after stirring 22 hr at room temperature. All the volatile materials in the solution were removed under vacuum and a deep dark green liquid was obtained and was identified as a mixture of *p*-methylphenyldisulfide **5-25** and *p*-toluenethiol-*p*-toluenesulfonate **5-26**, NMR, ^{1}H δ: 7.49-7.07 (m), 2.34-2.30 (m); ^{13}C δ: 138.8 -128.4 (m, C_{ar}), 21.2-21.1 (m, CH_3); MS [IE, 70eV] *m/z* (%): 278 (31, **5-26**), 256 (15, S_8), 246 (38, **5-25**), 214 (12), 155 (43), 123 (80), 91 (100).

N,N-Bis(trimethylsilyl)-*p*-toluenesulfinamide **(5-29)** (3.9 g, 13 mmol) was dissolved in 40 ml dry toluene to give a clear yellow solution and chlorocarbonylsulphenyl chloride (3.6 g, 28 mmol) was added into the solution under nitrogen at room temperature. The solution immediately turned to an orange color, eventually turning to a brown and dark brown-red color. After the solution was heated at 80-95°C for 7 hr, a cloudy orange solution was obtained. A yellowish white solid was filtered off to give a clear red-orange solution. The solid was identified as cyanuric acid **5-27** (0.5 g, 30%), m.p. >400°C, IR (cm^{-1}): 3147 (s), 3050 (s), 1764 (ms), 1721 (ms), 1409 (s). A mixture of a solid and a red liquid was obtained by removing the solvent and excess ClSC(O)Cl from the filtrate and the mixture was redissolved in $CHCl_3$ and passed through a column (silica gel, mesh 240-400). An orange liquid was received from the column and was identified (NMR and MS) as the disulfide **5-25** (1.6 g, 50%). A

colorless solid was also received from the column and identified (NMR and MS) as compound **5-26** (0.9 g, 25%).

5.2.6. Reaction of *N,N*-Bis(trimethylsilyl)-*p*-toluenesulfinamide with Mesitylnitrile Oxide

N,N-Bis(trimethylsilyl)-*p*-toluenesulfinamide (**5-29**) (2.1 g, 7.0 mmol) and mesitylnitrile oxide **5-31** (1.2 g, 7.3 mmol) were dissolved in methylene chloride (50 mL) under argon to give a clear colorless solution. The solution was stirred at room temperature for 96 hr. and no significant change was observed. By removing the solvent, all the starting materials were recovered.

5.2.7. Reaction of Benzosulfonamide with ClSC(O)Cl

Benzosulfonamide **5-21** [R = Ph, R' = H, X = S(O)] (5.0 g, 32 mmol) was mixed with dry toluene (40 mL) to give a white suspension. Chlorocarbonylsulfenyl chloride (5.2 g, 40 mmol) was added to the suspension. The resulting mixture was refluxed for 12 hr and no significant change was observed. A white solid (4.8 g) was filtered off and a yellow solution was obtained. The solid was identified as the unreacted amide (>95%). The solution did not leave significant amount of materials after the solvent was removed.

5.2.8. Reaction of *p*-Toluenesulfonamide with ClSC(O)Cl

p-Toluenesulfonamide **5-21** [R = *p*-$CH_3C_6H_4$, R' = H, X = S(O)] (2.4 g, 14 mmol) was mixed with dry chlorobenzene (30 mL) to give a white suspension. Chlorocarbonylsulfenyl chloride (4.7 g, 36 mmol) was added to the suspension and the suspension turned to a clear yellow solution. The solution was heated at 120°C for 48 hr. The solvent and excess ClSC(O)Cl were removed under vacuum and a yellowish

white solid (2.4 g) was obtained. The solid was identified as the unreacted amide with a very small amount of impurity.

5.2.9. Reaction of Adamantyl Phosphaalkyne with S_8

Adamantyl phosphaalkyne **5-37** (prepared by following the literature procedure[172]) (R = $C_{10}H_{15}$, 1.0 g, 5.6 mmol) and elemental sulphur (0.19 g, 5.9 mmol) were mixed in dry toluene (22 mL) under argon to give a clear colorless solution over a yellow solid. The mixture was stirred at 90-100°C for 16.5 hr. The solution turned into clear yellow while the solid remained unchanged. The solution was divided into two halves. One half was used for the further reaction described below. The other half was allowed to evaporate in the fumehood to give colorless crystals and a yellow sticky solid (0.46 g), NMR, ^{31}P δ: -65.9 (C≡P), 22.7, 24.9, 36.6, 39.1, 45.2; ^{13}C δ: 184.4 (d, 36.01 Hz), 128.7 (d, 61.03 Hz), 125.0 (s), 43.3-42.9 (m), 36.0-35.4 (m), 28.2-27.6 (m); ^{1}H δ: 1.93-1.58 (m); MS [IE, 70eV] *m/z* (%): 256 (1, S_8), 214 (2), 211 (0.1), 192 (1), 178 (100, RC≡P), 149 (17), 145 (16), 135 (65), 91 (63), 79 (66).

Triethylamine (freshly distilled over CaH_2, 6 mL) was added to the other half of the resulting mixture from the above reaction and the mixture was stirred at room temperature for 10 hr. No significant change was observed. The solvent was then removed and a yellow solid was obtained (0.82 g). The solid was redissolved in $CHCl_3$ and passed through a column (silica gel, mesh 240-400) eluted first by $CHCl_3$ and then acetone. A yellow solid was first recovered (0.22 g) from the column, MS [IE, 70eV] *m/z* (%): 294 (5), 256 (14, S_8), 214 (3), 192 (6), 178 (11), 160 (11), 135 (63), 128 (26),

96 (20), 91 (76), 64 (100), 39 (39), 32 (33). A second grey solid was also recovered from the column (the color changed in the column from the original yellow), 0.25 g, m.p. 224-225°C, MS [IE, 70eV] *m/z* (%): 86 (7), 85 (41), 83 (67), 58 (18), 48 (10), 47 (28), 43 (100), 35 (12), 34 (11), 32 (20), 28 (88).

5.3. Results and Discussion

5.3.1. Preparation of *p*-Toluenesulfinamide

p-Toluenesulfinamide *p*-$CH_3C_6H_4S(O)NH_2$ was first reported by Braun and Kaiser[145] in 1923. The method they used was the reaction of sulfinyl chloride with liquid ammonia and no detail was given for the process. The reaction was widely used[146-151] since then for the synthesis of the sulfinamide which had practical use such as a fog inhibitor in silver halide photography[150] and a component of a catalyst systems for the spinnable solutions of acrylonitrile polymers[150]. The only details described for the reaction were that a solvent such as diethyl ether[146,151] was used and the reaction temperature was at 0°C[151]. No yield was reported in any of the accounts.

The reaction of *p*-toluenesulfinyl chloride with liquid ammonia was examined in dry diethyl ether at -78°C - 0°C. The reaction was extremely vigorous and it was very difficult to control the reaction because the evaporation of ammonia (b.p. -33°C) carried the solvent off quickly and large amounts of solid immediately formed from the reaction that made stirring impossible. The yield of the amide from the reaction was unacceptably low (0% - 5%) while the yield of the by-product *p*-toluenedisulfide *p*-$CH_3C_6H_4S$-$SC_6H_4CH_3$-*p* was high. The reaction was improved significantly when the ammonia was very slowly bubbled through a dilute diethyl ether solution of *p*-toluenesulfinyl chloride. A large amount of solvent was required to make the solution dilute since both the product amide and the by-product ammonium chloride were insoluble and the solvent itself

diminished gradually during the reaction. The slow passage of the ammonia gas was to slow down the vigorous reaction. The yield of the improved reaction is 45%.

5.3.2. Preparation and Structure of *N,N*-Bis(trimethylsilyl)-*p*-toluenesulfinamide

There have been only two reports[152-153] on the synthesis and chemistry of *N,N*-bis(trimethylsilyl)-*p*-toluenesulfinamide *p*-$CH_3C_6H_4S(O)$-$N(SiMe_3)_2$ **5-29**. It was first prepared by Wenschuh and Fritzsche[152] in 1970. They converted *p*-toluenesulfinamide *p*-$CH_3C_6H_4S(O)NH_2$ with n-butyllithium into its mono-lithium amide which reacted with chlorotrimethylsilane to form *N*-trimethylsilyl-*p*-toluenesulfinamide *p*-$CH_3C_6H_4S(O)$-$NH(SiMe_3)$. The latter was again converted into the lithium amide and then reacted with chlorotrimethylsilane to give the amide **5-29** with a yield of 75%. Golebiowski and Lasocki[153] performed a ^1H NMR study on the mono *N*-silylamide along with other aromatic mono *N*-silylamides. They found that there was no indication that N-O-silyl migration occurred for these compounds at different temperatures while the migration is a common phenomenon for most bis(trimethylsilyl)carbonamides (see Chapter 4.3.2). The reaction used in this work was that of *p*-toluenesulfinyl chloride with lithium bis(trimethylsilyl)amide and the yield of the product *N,N*-bis(trimethylsilyl)-*p*-toluenesulfinamide was about 76%. This method is undoubtedly better than the one above which contained multi-step reactions despite of the difficulties in the synthesis of *p*-toluenesulfinamide.

Structural studies on bis(trimethylsilyl)carbonamides[113-124] [$RC(O)$-$N(SiMe_3)_2$] **4-6** and bis(trimethylsilyl)carbonyl phosphines[154-159] [$RC(O)$-$P(SiMe_3)_2$] **5-33** have revealed that

1,3-migration of trimethylsilyl groups from nitrogen to oxygen or from phosphorus to oxygen in these amide-like compounds is favourable at room temperature. Therefore the structures of most bis(trimethylsilyl)carbonamides and bis(trimethylsilyl)carbonyl phosphines are in their imidol forms [$RC(OSiMe_3)=NSiMe_3$) **4-7** or $RC(OSiMe_3)=PSiMe_3$) **5-34**] at room temperature. The structure of a bis(trimethylsilyl)sulfinamides, however, has not been reported before. A ^1H NMR study of bis(trimethylsilyl)-*p*-toluenesulfinamide **5-29** was carried out in order to obtain structural information. The result (Appendix 7) showed that there was only one major peak of the trimethylsilyl group at 0.17 ppm (corresponding to the peak of CH_3 at 2.83 ppm of its ^{13}C NMR spectrum) at -10° to +60°C. It was observed however that the peak split into two singlets with a difference of ~0.2 ppm at -40°C and below. One of the split singlets remained at about the same position and the other was observed at higher field. Previous NMR studies[160-162] of *N,N*-substituted sulfinamides showed that there is always a weak pπ - dπ delocalization between the nitrogen and the sulphur and aromatic rings will decrease this double bond character due to the resonance conjugation of the sulphur with the aromatic ring. The ^1H NMR spectrum of *N,N*-Bis(trimethylsilyl)-*p*-toluenesulfinamide **5-29** in this work had one singlet for its trimethylsilyl group at room temperature which was consistent with the methyl group in *N,N*-dimethyl-*p*-toluenesulfinamide[160]. It is reasonable to believe that the amide **5-29** is in the keto form and it has free rotation along the N-S bond due to the weakened pπ - dπ delocalization between N and S at room temperature and above. It can, however, adopt the imidol form **5-30** with the assistance

of the favourable 1,3-migration of the trimethylsilyl group at the lower temperature. It also strongly suggests that the S=N double bond in this enol form of the amide **5-30** is much weaker compared to the C=N and C=P double bonds in their enol forms (**4-7** and **5-34**).

5.3.3. Reactions of Sulfinamides, Bis(trimethylsilyl)sulfinamides with ClSC(O)Cl

The reactions of sulfinamides or bis(trimethylsilyl)sulfinamides with ClSC(O)Cl were designed for the preparation of the proposed unknown precursor 1,3,5,4-oxadithiazol-2-one **5-22** (X = S) which was supposed, upon heating or irradiation, to generate the very unstable intermediate thiazyl sulphide **5-23**, a novel inorganic 1,3-dipole containing sulphur and nitrogen as its component atoms of the π manifold. As mentioned in the introduction, the new 1,3-dipole was assumed to be similar in structure and bonding to the known nitrile sulphides. Since nitrile sulphides could not be isolated under normal conditions, the proposed thiazyl sulphides, if they could be prepared, would probably be unstable as well. New stable precursors must also be required for the *in situ* generation of these new 1,3-dipoles in a synthetic sequence derived from that of the oxathiazolones for nitrile sulphides (Scheme 5-3).

The reaction of *p*-toluenesulfinamide [*p*-$CH_3C_6H_4S(O)NH_2$] with ClSC(O)Cl in hot toluene gave *p*-toluenedisulfide **5-25** [*p*-$CH_3C_6H_4S$-$SC_6H_4CH_3$-*p*], *p*-toluenethiol-*p*-toluenesulfonate **5-26** [*p*-$CH_3C_6H_4S(O)_2$-$SC_6H_4CH_3$-*p*], and cyanuric acid **5-27** in 49%, 22%, and 57% yields respectively. There was no indication that the proposed precursor 1,3,5,4-oxadithiazol-2-one **5-22** (X = S) was generated from the reaction. No apparent

reaction occurred between the amide and ClSC(O)Cl in cold toluene (-23° - 0°C) and the insoluble amide was recovered quantitatively. Bis(trimethylsilyl)-*p*-toluenesulfinamide **5-29** was then examined. The reaction of this amide with ClSC(O)Cl both in cold $CHCl_3$ and hot toluene gave *p*-toluenedisulfide **5-25** and *p*-toluenethiol-*p*-toluenesulfonate **5-26**. Cyanuric acid **5-27** was the only product obtained from the reaction in hot toluene in 30% yield. These results can be explained by the homolytic cleavage of the weak S-N bond in the amides and followed by radical chain reactions such as the dimerization, recombination and disproportionation of sulfinyl radicals[163] [RS(O)·] which can be generated from sulfinic acids[164], sulfinates[165], and sulfinamides[166-167] upon heating or radiating with light. The disulfides and sulfonate thio-esters are the regular products of these radical reactions. Cyanuric acid can be formed on heating urea[168] and was formed only from these hot reactions of sulfinamides with ClSC(O)Cl. It is now clear that sulfinamides cannot be used to react with ClSC(O)Cl under these or any conditions to form the precursor **5-22** (X = S) because of the weak S-N bonds in these amides. It is necessary to find another method to synthesize the precursor or to discover other precursors or reactions to generate a derivative of the thiazyl sulphides **5-23** (X = S).

5.3.4. Reaction of Bis(trimethylsilyl)-*p*-toluenesulfinamide with Mesitylnitrile Oxide

Regitz and co-workers[169] discovered that *P,O*-bis(trimethylsilyl)carbonyl phosphines R-C(OTMS)=P-TMS (so-called phosphaalkenes) could react with nitrile oxides, reactive but isolable 1,3-dipoles, to form the five-membered heterocycles 1,2,4-oxazaphospholes. The reaction was confirmed by Copp[170] working in this laboratory. He

found that bis(1,2,4-oxazaphosphole) could be prepared from the reaction of the corresponding bis(phosphaalkene) with a nitrile oxide. This reaction is also an useful means to generate the *synthetic equivalent*[1] of phosphaalkynes. The reaction of bis(trimethylsilyl)-*p*-toluenesulfinamide **5-29** with mesitylnitrile oxide **5-31** was set up for the same purpose: generation of the synthetic equivalent of *p*-toluenethiazyne (*p*-$CH_3C_6H_4S{\equiv}N$). The reaction was carried out at room temperature and no apparent reaction occurred between the two starting materials. There are two major reasons for it. First, bis(trimethylsilyl)-*p*-toluenesulfinamide **5-29** may be in its keto form at room temperature (see chapter 5.3.2) which could affect the reaction and a lower temperature would affect the reactivity of the nitrile oxide. Secondly, both the thiazyne and the nitrile oxide are electron rich species which is unfavourable to the cycloaddition reaction. From Figure 1-3, it is clear that the 1,3-dipolar cycloaddition reaction depends on the energy gap between usually[52] the HOMO of the dipole and the LUMO of the dipolarophile. The 1,3-dipolar cycloaddition reaction of an electron rich 1,3-dipole with an electron poor dipolarophile would therefore more favourable and *vice versa*. From this point of view, introducing electron withdrawing groups to the thiazyne should make the reaction of mesitylnitrile oxide with the thiazyne more favourable.

5.3.5. Reaction of Sulfonamides with ClSC(O)Cl

The reactions of sulfonamides with ClSC(O)Cl were designed for the preparation

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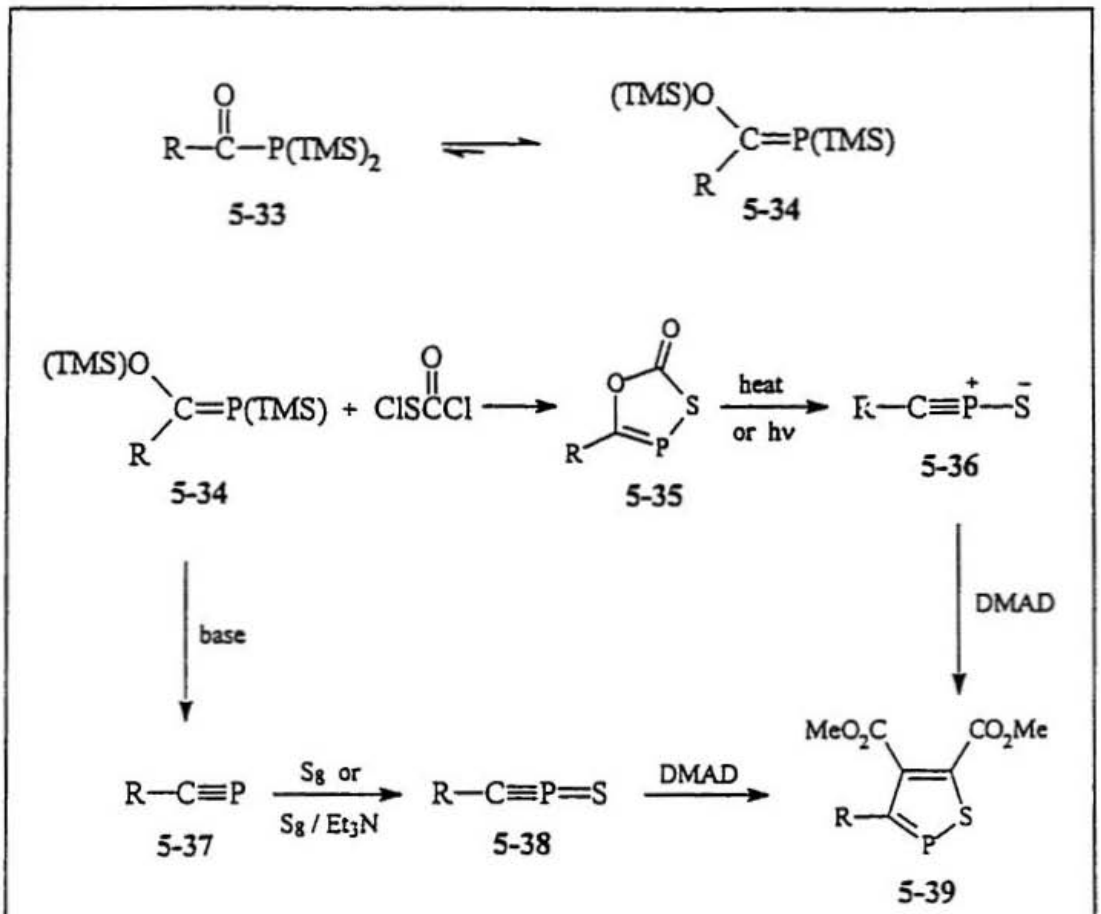
[1] Compounds are **synthetically equivalent** when their reactions produce the same product(s) even though they feature different compositions and structures.

of a currently unknown precursor 1,3,4-oxathiazol-5-thioxide-2-one **5-22** [X = S(O)]. The precursor was suggested, upon heating or irradiation, to generate another very unstable intermediate thioxidazyl sulphide **5-23** [X = S(O)], another novel inorganic 1,3-dipole containing sulphur and nitrogen as its component atoms. Unfortunately, the two selected sulfonamides, benzosulfonamide [$C_6H_5S(O)_2NH_2$] and *p*-toluenesulfonamide [*p*-$CH_3C_6H_5S(O)_2NH_2$] did not react with ClSC(O)Cl even in refluxing toluene and chlorobenzene. Solubility was not a problem because *p*-toluenesulfonamide completely dissolved in chlorobenzene upon the addition of ClSC(O)Cl and the amide was fully recovered from the solution after 48 hr of heating. The results suggest that the expected reaction between the selected sulphonamides with chlorocarbonylsulfenyl chloride will not occur. This might be due to the weak acidity of the sulfonamides (pK_a values are 10.07 and 10.21 at 20°C for benzosulfonamide and *p*-toluenesulfonamide respectively[175]). Chlorocarbonylsulfenyl chloride is acid sensitive and will decompose at an acidic solution.

5.3.6. Generation of Phosphaalkyne Sulphides

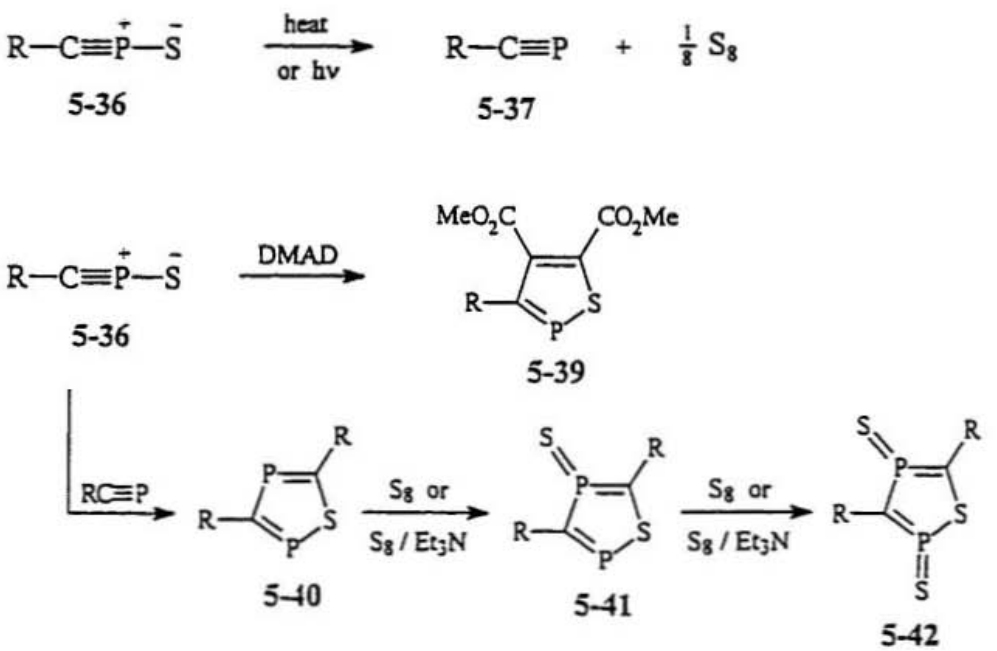
The phosphaalkyne sulphide, **5-36**, a new 1,3-dipolar analogue of nitrile sulphides, was first proposed as the intermediate in the reaction of oxathiazolone **5-13** with phosphaalkene **5-14** but was actually not generated from the reaction (see 5.1). This 1,3-dipole contains phosphorus, another heavy *p* block element besides sulphur which is well known in 1,3-dipole systems. The phosphaalkyne sulphide was initially thought as an unstable intermediate **5-36** just like the nitrile sulphide so that the unknown precursor 1,3,4-oxathiophosphole-2-one **5-35** was designed for it. The strategy of making the



Scheme 5-5. Two proposed synthetic routes to phosphaalkyne sulphides

precursor is similar to that for oxathiazolones discussed in chapter 4. The reaction of phosphaalkenes **3-34**, the favourable form of carbonyl phosphines **5-33**, was supposed to react with ClSC(O)Cl to form the precursor **5-35** which would generate the 1,3-dipole **5-36** upon heating or radiating (Scheme 5-5). Based on the well developed chemistries (mainly decomposition and cycloaddition reactions) of nitrile sulphides (see previous chapters), the new 1,3-dipole phosphaalkyne sulphide **5-36**, if generated, may be trapped by dipolarophiles such as DMAD and phosphaalkynes **5-37** or may decompose to the phosphaalkyne and elemental sulphur. Other possible reactions may also take place based on the known chemistries of low coordination phosphorus compounds[70] (Scheme 5-6). The reaction of phosphaalkenes (R = adamantyl and *t*-butyl) with ClSC(O)Cl, unfortunately, remains unknown after several years effort[173].

The reactions of elemental sulphur (S_8) with organic compounds are well documented[174]. It is also not new that phosphorus (III) compounds (e.g. R_2PH, $R^1R^2C{=}PR^3$, $RP{=}PR'$, and phosphacubene) can react with elemental sulphur with or without a catalyst (such as Et_3N) to form the corresponding phosphorus (V) sulphides[70,176-179] [e.g. $R_2HP{=}S$, $R^1R^2C{=}P(S)R^3$, $RP{=}P(S)R'$]. Most of these phosphorus (V) sulphides are air and moisture stable with a few that are water sensitive[176]. Phosphaalkynes are also σ^1,λ^3-phosphorus compounds (σ^1 = one-coordinate, λ^3 = trivalent) and there has been no report on their corresponding σ^2,λ^5-phosphorus sulphides (e.g. $RC{\equiv}P{=}S$) or oxides (e.g. $RC{\equiv}P{=}O$)[70,180]. The reaction of phosphaalkynes ($RC{\equiv}P$) with elemental sulphur has also not been reported before[180]. If phosphaalkyne sulphides **5-36** are actually stable as the



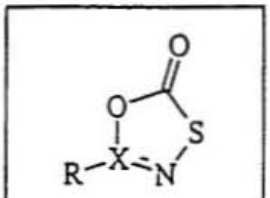
5-36 5-37 5-36 5-39 5-40 5-41 5-42

Scheme 5-6. Some proposed reactions for phosphaalkyne sulphides

phosphorus (V) compound **5-38**, it will not be necessary to prepare the precursors such as 1,3,4-oxathiophosphole-2-one **5-35** and the phosphaalkyne sulphides **5-38** themselves can be targeted directly by using reactions like that of phosphaalkynes with elemental sulphur. The pπ - dπ bonding of P-S bond in the phosphaalkyne sulphides **5-38** are weak compared to the phosphaalkyne oxides (RC≡P=O) because of the low electronegativity of sulphur and the weak π delocalization. This might in fact augment their behaviour as 1,3-dipoles towards dipolarophiles. To test this argument, the reactions of adamantyl phosphaalkyne ($C_{10}H_{15}C{\equiv}P$) with elemental sulphur in hot toluene and in cold toluene in the presence of triethylamine were examined. The ^{31}P NMR spectrum showed that adamantyl phosphaalkyne was recovered >90% from the hot toluene reaction without the catalyst triethylamine along with a small amount unknown product(s) containing phosphorus. The mass spectrum of the products mixture did not give indicate that any of the desired product adamantyl phosphaalkyne sulphide (*m/z* 210) had been generated. The ^{31}P NMR showed that some minor products containing P (δ = 22.7 - 45.2 ppm) were generated from the reaction. The phosphaalkyne sulphides **5-38**, if generated, should appear at a lower field than their corresponding phosphaalkynes (δ = +96 to -207 ppm, mostly between +35 to -70 ppm)[175] because the phosphorus nucleus is greatly deshielded in the two-coordinate phosphorus (V) than in the one-coordinate phosphorus (III). Since the δ (^{31}P) value of adamantyl phosphaalkyne is at -66 ppm, adamantyl phosphaalkyne sulphide should appear at lower field than it (e.g. δ > -66 ppm). The reaction is, however, still not clear based on the complicated spectra.

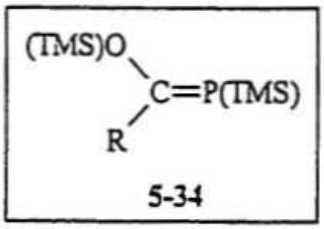
Triethylamine was added to part of the above reaction mixture and the newly mixed solution was stirred for another 10 hr at room temperature. The crude product was passed through a column and two major products were recovered. None of them gave the fragment at *m/z* 210 (adamantyl phosphaalkyne sulphide) in their mass spectra and their NMR spectra were even more complicated. The attempts to synthesize adamantyl phosphaalkyne sulphide in this work were inconclusive. The reactions of phosphaalkynes with elemental sulphur, however, still need to be examined at different conditions because this type of reaction has not been reported before and σ^2,λ^5-phosphorus compounds, to my knowledge, are still missing from the chemistry of the low coordinate phosphorus compounds[70,180].

In conclusion, attempts to generate unknown 1,3-dipoles containing sulphur as the central atom (R-S≡N$^+$-S$^-$ and R-S(O)≡N$^+$-S$^-$) in the π systems through thermal decomposition reactions of the proposed precursors **5-22** are not completed. These heterocycles **5-22** could not be prepared via the reaction of sulfinamide/sulfonamides or their bis(trimethylsilyl) derivatives with chlorocarbonylsulfenyl chloride.

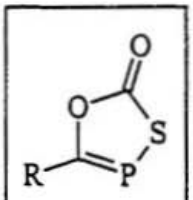


5-22 [X = S, S(O)]

Other reactions to generate these inorganic 1,3-dipoles should be considered in the future. Similarly the reaction of adamantyl phosphaalkene **5-34** with chlorocarbonylsulfenyl chloride did not give heterocycle **5-35** which might eventually generate phosphaalkyne sulphide **5-36**, another unknown 1,3-dipole. The reaction of

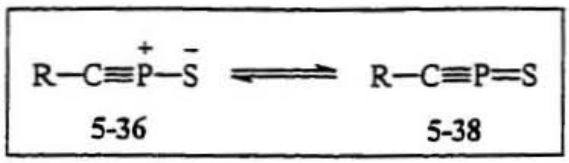


5-34



5-35

phosphaalkynes with elemental sulphur, however, to synthesize a stable species, also phosphaalkyne sulphides **5-38**, is still my personal hope for the future generation of the compounds sought in this thesis. The unknown species **5-23** and **5-36/3-38**, if they could be generated, would challenge classical multiple π bonding theory and open a door to a wonderful new chemistry.



5-36 **5-38**

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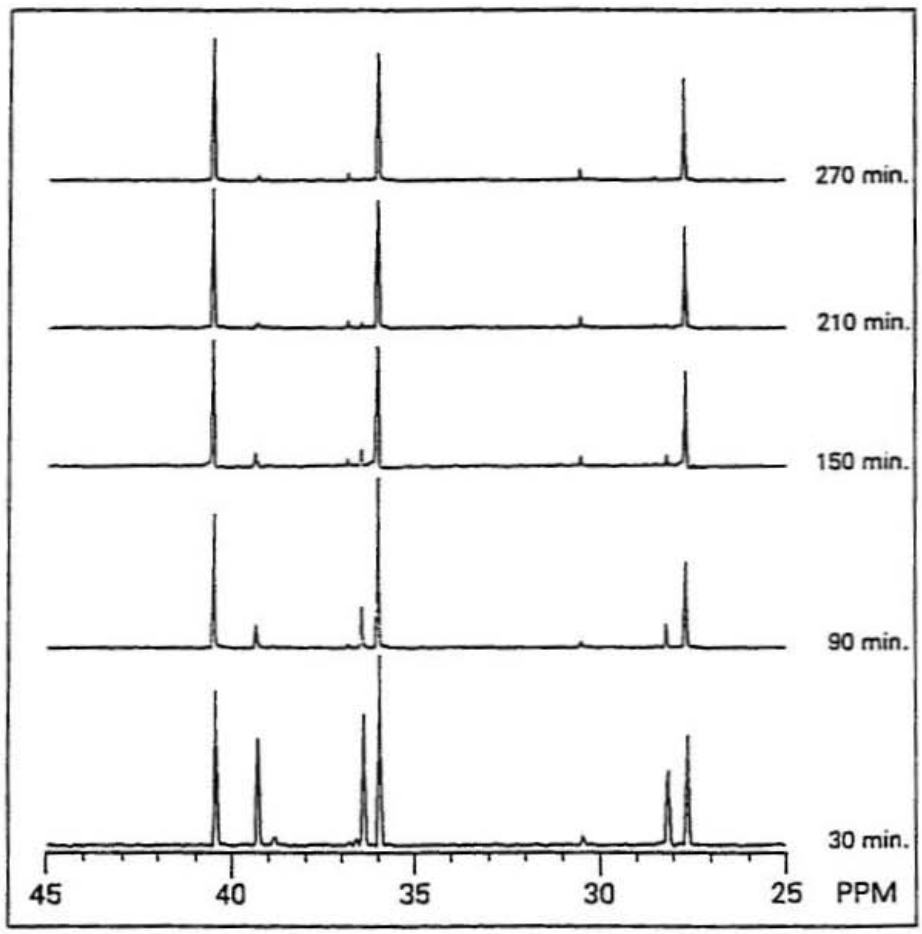
Appendix 1 ^{13}C NMR spectra (kinetic run) of the reaction of 5-adamantyl-1,3,4-oxathiazol-2-one **2-5** with adamantyl nitrile



Appendix 2 X-Ray Crystal Structures of 2-7, 3-27a to 3-47, 4-4c.

Table A2-1 Crystallographic Data for 2-7, 3-27a to 3-47, 4-4c

Compound	Data
2-7	$C_{17}H_{21}NO_4S$ (F.W. 335.42), monoclinic, $P2_1/c$ (#14), a = 7.305(4) Å, b = 7.339(4) Å, c = 31.552(4) Å, β = 92.75(3)°, V = 1690(1) Å^3, Z = 4, D_{calcd} = 1.318 g/cm^3, size: 0.40 x 0.30 x 0.20 mm, μ = 18.25 cm^{-1}, R = 0.072, R_w = 0.079
3-27a	$C_{12}H_{18}N_2O_2$ (F.W. 222.29), monoclinic, C2/c (#15), a = 7.934(3) Å, b = 15.543(3) Å, c = 9.404(2) Å, β = 93.63(2)°, V = 1157.4(5) Å^3, Z = 4, D_{calcd} = 1.276 g/cm^3, size: 0.30 x 0.30 x 0.23 mm, μ = 0.82 cm^{-1}, R = 0.039, R_w = 0.040
3-29a	$C_{13}H_{14}N_2O_2S$ (F.W. 262.33), monoclinic, $P2_1/c$ (#14), a = 9.153(2) Å, b = 19.134(2) Å, c = 7.130(3) Å, β = 105.38(2)°, V = 1204(1) Å^3, Z = 4, D_{calcd} = 1.447 g/cm^3, size: 0.40 x 0.40 x 0.08 mm, μ = 2.52 cm^{-1}, R = 0.038, R_w = 0.035
3-28b	$C_{12}H_{16}N_2O_4S_2$ (F.W. 316.39), monoclinic, $P2_1/c$ (#14), a = 11.183(2) Å, b = 5.077(3) Å, c = 13.107(3) Å, β = 106.62(2)°, V = 713.0(5) Å^3, Z = 2, D_{calcd} = 1.474 g/cm^3, size: 0.40 x 0.20 x 0.08 mm, μ = 3.71 cm^{-1}, R = 0.041, R_w = 0.035
3-31	$C_{24}H_{26}N_2O_8S_2$ (F.W. 534.60), orthorhombic, $Pca2_1$ (#29), a = 15.857(4) Å, b = 11.562(4) Å, c = 13.602(4) Å, V = 2494(2) Å^3, Z = 4, D_{calcd} = 1.424 g/cm^3, size: 0.40 x 0.35 x 0.20 mm, μ = 2.53 cm^{-1}, R = 0.057, R_w = 0.038
3-32	$C_{13}H_{20}N_2O_4S$ (F.W. 360.43), monoclinic, $P2_1/c$ (#14), a = 19.683(2) Å, b = 11.566(3) Å, c = 7.727(3) Å, β = 93.30(2)°, V = 1756(1) Å^3, Z = 4, D_{calcd} = 1.363 g/cm^3, size: 0.30 x 0.25 x 0.15 mm, μ = 1.99 cm^{-1}, R = 0.079, R_w = 0.076
3-41	$C_{11}H_6N_2O_2S_2$ (F.W. 262.30), monoclinic, $P2_1/c$ (#14), a = 9.738(4) Å, b = 9.990(3) Å, c = 11.216(3) Å, β = 90.39(3)°, V = 1091.1(6) Å^3, Z = 4, D_{calcd} = 1.597 g/cm^3, size: 0.30 x 0.30 x 0.10 mm, μ = 4.56 cm^{-1}, R = 0.051, R_w = 0.047
3-42	$C_{11}H_6N_2O_2S_2$ (F.W. 262.30), triclinic, P1 (#2), a = 11.273(4) Å, b = 14.691(3) Å, c = 7.289(3) Å, α = 101.68(2)°, β = 108.33(3)°, γ = 87.56(2)°, V = 1121.8(6) Å^3, Z = 4, D_{calcd} = 1.553 g/cm^3, size: 0.40 x 0.20 x 0.40 mm,

Table A2-1 Crystallographic Data for 2-7, 3-27a to 3-47, 4-4c (continued)

Compound	Data
3-42	μ = 4.43 cm^{-1}, R = 0.045, R_w = 0.046
3-43	$C_{15}H_{12}N_2O_2S_2$ (F.W. 316.39), monoclinic, $P2_1/c$ (#14), a = 13.481(5) Å, b = 9.138(4) Å, c = 13.399(4) Å, β = 111.29(3)°, V = 1538(2) $Å^3$, Z = 4, D_{calcd} = 1.366 g/cm^3, size: 0.40 x 0.20 x 0.40 mm, μ = 3.35 cm^{-1}, R = 0.041, R_w = 0.039
3-46	$C_{15}H_{12}N_2O_2S_2$ (F.W. 316.39), monoclinic, $P2_1/c$ (#14), a = 13.047(3) Å, b = 11.222(4) Å, c = 9.904(3) Å, β = 93.45(2)°, V = 1447(1) $Å^3$, Z = 4, D_{calcd} = 1.452 g/cm^3, size: 0.30 x 0.20 x 0.20 mm, μ = 3.56 cm^{-1}, R = 0.042, R_w = 0.039
3-47	$C_{15}H_{12}N_2O_2S_2$ (F.W. 316.39), monoclinic, $P2_1/c$ (#14), a = 10.873(4) Å, b = 32.96(1) Å, c = 8.635(5) Å, β = 104.18(4)°, V = 3000(4) $Å^3$, Z = 4, D_{calcd} = 1.401 g/cm^3, size: 0.40 x 0.20 x 0.15 mm, μ = 3.44 cm^{-1}, R = 0.066, R_w = 0.056
4-4c	$C_{14}H_9NO_2S$ (F.W. 255.29), orthorhombic, Pbca (#61), a = 25.243(3) Å, b = 11.359(3) Å, c = 8.167(3) Å, V = 2342(2) $Å^3$, Z = 8, D_{calcd} = 1.448 g/cm^3, size: 0.40 x 0.30 x 0.20 mm, μ = 2.55 cm^{-1}, R = 0.040, R_w = 0.034

[a] Least-squares refinement of $[(\sin\theta)/\lambda]^2$ for 24 reflections $\theta > 14°$

[b] $I > 1\sigma(I)$ or $2\sigma(I)$. Corrections: Lorentz-polarization and absorption (empirical psi scan)

[c] Neutral scattering factors and anomalous dispersion corrections from *d*

[d] An Interactive Program System for Structure Analysis, E.J. Gabe, Y. Le Page, J-P. Charland, F.L. Lee and P.S. White, *J. Appl. Cryst.*, **22**, 384, 1989

[e] More details see reference 81.

Appendix 2 X-Ray Crystal Structures of 2-7, 3-27a to 3-47, 4-4c.

Table A2-2 Selected Bond Lengths (Å) for 2-7, 3-27a to 3-47, 4-4c

Compound	Bond Lengths					
2-7	S(1)-N(1):	1.645(4)	S(1)-C(3):	1.690(4)	O(1)-C(14):	1.186(6)
	N(1)-C(1):	1.323(6)	C(1)-C(2):	1.429(6)	O(2)-C(14):	1.323(6)
	C(1)-C(4):	1.524(6)	C(2)-C(3):	1.370(6)	O(2)-C(15):	1.470(9)
3-27a	O(1)-C(7):	1.235(2)	N(1)-C(7):	1.326(2)	C(1)-C(2):	1.533(3)
	C(1)-C(5):	1.542(2)	C(1)-C(6):	1.547(3)	C(1)-C(7):	1.525(2)
	C(2)-C(3):	1.530(3)	C(3)-C(4):	1.524(3)	C(3)-C(6):	1.533(3)
3-29a	S(1)-N(1):	1.691(2)	S(1)-C(2):	1.753(3)	O(1)-C(1):	1.374(3)
	O(1)-C(2):	1.396(3)	O(2)-C(2):	1.174(3)	N(2)-C(13):	1.139(3)
	N(1)-C(1):	1.276(3)	C(1)-C(3):	1.499(3)	C(3)-C(4):	1.535(3)
	C(3)-C(8):	1.551(3)	C(4)-C(5):	1.532(3)	C(5)-C(6):	1.526(3)
	C(6)-C(7):	1.528(4)	C(7)-C(8):	1.530(3)	C(7)-C(12):	1.528(4)
	C(9)-C(10):	1.539(3)			C(10)-C(11):	1.536(3)
	C(10)-C(12):	1.544(4)			C(10)-C(13):	1.474(4)
	C(3)-C(9):	1.543(3)				
3-28b	S(1)-N(1):	1.695(3)	S(1)-C(1):	1.743(3)	O(1)-C(1):	1.393(3)
	O(1)-C(2):	1.377(3)	O(2)-C(1):	1.186(3)	N(1)-C(2):	1.260(4)
	C(2)-C(3):	1.484(4)	C(3)-C(4):	1.515(4)	C(4)-C(5):	1.513(4)
	C(5)-C(6):	1.512(4)	C(6)-C(6'):	1.516(6)		
3-31	S(1)-N(1):	1.646(6)	S(1)-C(3):	1.716(7)	S(2)-N(2):	1.650(6)
	S(2)-C(6):	1.709(7)	O(1)-C(17):	1.324(9)		
	O(1)-C(18):	1.448(8)			O(2)-C(17):	1.198(8)
	O(3)-C(19):	1.163(8)			O(4)-C(19):	1.347(8)
	O(4)-C(20):	1.462(9)			N(1)-C(1):	1.315(7)
	N(2)-C(4):	1.312(7)	C(1)-C(2):	1.451(8)	C(1)-C(9):	1.531(8)
	C(2)-C(3):	1.371(8)	C(4)-C(5):	1.419(9)	C(2)-C(17):	1.500(9)
	C(4)-C(7):	1.523(9)	C(5)-C(6):	1.365(9)	C(3)-C(19):	1.49(1)
	C(5)-C(21):	1.504(9)			C(6)-C(23):	1.48(1)
	C(7)-C(8):	1.540(8)	C(7)-C(12):	1.542(9)		
	C(8)-C(9):	1.550(8)	C(7)-C(13):	1.527(9)		
3-32	S(1)-N(1):	1.659(5)	S(1)-C(3):	1.692(7)	O(1)-C(14):	1.200(7)
	O(2)-C(14):	1.354(8)			O(2)-C(15):	1.437(8)
	O(3)-C(16):	1.195(7)			O(4)-C(16):	1.315(8)

Table A2-2 Selected Bond Lengths (Å) for 2-7, 3-27a to 3-47, 4-4c(continued)

Compound	Bond Lengths			
3-32	N(1)-C(1): 1.281(7)	C(1)-C(2): 1.441(9)	O(4)-C(17): 1.473(8)	
	C(1)-C(4): 1.536(9)	C(2)-C(3): 1.371(8)	C(2)-C(14): 1.482(9)	
	C(4)-C(5): 1.547(9)	C(4)-C(9): 1.540(9)	C(3)-C(16): 1.504(9)	
	C(5)-C(6): 1.566(9)	C(6)-C(7): 1.51(1)	C(4)-C(10): 1.546(8)	
	C(6)-C(13): 1.550(9)		C(6)-C(18): 1.49(1)	
3-41	S(1)-N(1): 1.686(4)	S(1)-C(1): 1.736(5)	S(2)-N(2): 1.658(4)	
	S(2)-C(4): 1.687(4)	O(1)-C(1): 1.380(5)	O(1)-C(2): 1.378(5)	
	O(2)-C(1): 1.199(5)	N(1)-C(2): 1.286(5)	N(2)-C(5): 1.322(5)	
	C(2)-C(3): 1.457(5)	C(3)-C(4): 1.381(6)	C(3)-C(5): 1.430(5)	
	C(5)-C(6): 1.473(6)	C(6)-C(7): 1.392(6)	C(6)-C(11): 1.389(6)	
	C(7)-C(8): 1.377(7)	C(8)-C(9): 1.377(7)	C(9)-C(10): 1.379(7)	
	C(10)-C(11): 1.378(7)			
3-42	S(1)-N(1): 1.677(3)	S(1)-C(1): 1.758(4)	N(1)-C(2): 1.279(4)	
	S(2)-N(2): 1.645(3)	N(2)-C(5): 1.327(4)	S(2)-C(3): 1.712(3)	
	C(3)-C(4): 1.363(5)	C(4)-C(5): 1.409(5)	C(5)-C(6): 1.482(5)	
	C(6)-C(7): 1.386(5)	O(1)-C(1): 1.379(4)	C(6)-C(11): 1.379(5)	
	C(7)-C(8): 1.377(5)	O(1)-C(2): 1.367(4)	C(8)-C(9): 1.376(6)	
	O(2)-C(1): 1.184(4)	C(9)-C(10): 1.371(6)		
	C(10)-C(11): 1.390(5)			
3-43	S(1)-N(1): 1.656(2)	S(1)-C(1): 1.684(3)	O(1)-C(13): 1.205(3)	
	S(2)-C(5): 1.692(3)	S(2)-N(2): 1.648(3)	O(2)-C(13): 1.323(3)	
	N(1)-C(3): 1.321(3)	N(2)-C(6): 1.326(3)	O(2)-C(14): 1.470(3)	
	C(1)-C(2): 1.361(4)	C(2)-C(3): 1.429(4)	C(2)-C(13): 1.481(3)	
	C(3)-C(4): 1.475(3)	C(4)-C(5): 1.362(3)	C(4)-C(6): 1.430(4)	
	C(6)-C(7): 1.479(4)	C(7)-C(8): 1.392(4)	C(7)-C(12): 1.389(4)	
	C(8)-C(9): 1.390(4)			
3-46	S(1)-N(1): 1.637(3)	N(1)-C(3): 1.679(3)	O(1)-C(13): 1.192(4)	
	S(2)-C(4): 1.711(3)	S(2)-N(2): 1.645(3)	O(2)-C(14): 1.475(4)	
	N(1)-C(1): 1.328(4)	N(2)-C(5): 1.316(4)	C(1)-C(2): 1.433(4)	
	C(1)-C(4): 1.475(4)	C(2)-C(3): 1.362(4)	C(2)-C(13): 1.482(4)	
	C(4)-C(6): 1.354(4)	C(5)-C(6): 1.422(4)	C(5)-C(7): 1.473(4)	
	C(7)-C(8): 1.384(4)	C(8)-C(9): 1.381(5)	C(7)-C(12): 1.386(4)	
3-47	S(1)-N(1): 1.640(7)	N(1)-C(1): 1.338(9)	S(1)-C(3): 1.713(7)	
	S(2)-C(4): 1.704(8)	S(2)-N(2): 1.649(7)	O(1)-C(13): 1.20(1)	

Table A2-2 Selected Bond Lengths (Å) for 2-7, 3-27a to 3-47, 4-4c (continued)

Compound	Bond Lengths					
3-47	N(1)-C(1):	1.338(9)	N(2)-C(5):	1.33(1)	O(2)-C(13):	1.34(1)
	C(1)-C(2):	1.40(1)	C(1)-C(4):	1.44(1)	C(2)-C(3):	1.36(1)
	C(4)-C(6):	1.37(1)	C(5)-C(6):	1.41(1)	C(3)-C(13):	1.46(1)
	C(5)-C(7):	1.48(1)	O(2)-C(14):	1.45(1)		
4-4c	S(1)-N(1):	1.682(2)	S(1)-C(1):	1.742(3)	O(1)-C(1):	1.193(3)
	O(2)-C(1):	1.392(3)	O(2)-C(2):	1.375(3)	N(1)-C(2):	1.276(3)
	C(2)-C(3):	1.461(4)	C(3)-C(4):	1.384(3)	C(3)-C(8):	1.384(4)
	C(4)-C(5):	1.381(4)	C(5)-C(6):	1.391(4)	C(6)-C(7):	1.396(3)

Appendix 2 X-Ray Crystal Structures of 2-7, 3-27a to 3-47, 4-4c.

Table A2-3 Selected bond Angles (°) for 2-7, 3-27a to 3-47, 4-4c

Compound	Bond Angles	
2-7	N(1)-S(1)-C(3): 94.7(2)	C(3)-C(2)-C(14): 121.7(4)
	S(1)-C(3)-C(2): 109.5(3)	S(1)-C(3)-C(16): 124.3(3)
	S(1)-N(1)-C(1): 111.1(3)	C(2)-C(3)-C(16): 126.2(4)
	N(1)-C(1)-C(2): 114.0(4)	C(1)-C(4)-C(5): 111.0(4)
	N(1)-C(1)-C(4): 117.6(4)	C(1)-C(4)-C(9): 106.7(4)
	C(2)-C(1)-C(4): 128.3(4)	C(1)-C(4)-C(10): 113.1(4)
	C(1)-C(2)-C(3): 110.8(4)	C(14)-O(1)-C(15): 114.0(4)
	C(5)-C(4)-C(9): 108.8(4)	C(16)-O(4)-C(17): 115.4(4)
3-27a	C(2)-C(1)-C(5): 108.8(1)	C(2)-C(1)-C(6): 108.9(2)
	C(2)-C(1)-C(7): 110.2(1)	C(5)-C(1)-C(6): 108.6(1)
	C(5)-C(1)-C(7): 112.1(2)	C(6)-C(1)-C(7): 108.1(1)
	C(1)-C(2)-C(3): 110.1(2)	C(2)-C(3)-C(4): 110.0(2)
	C(2)-C(3)-C(6): 109.5(2)	C(4)-C(3)-C(6): 110.1(2)
	C(3)-C(4)-C(3): 108.9(2)	C(1)-C(5)-C(1): 110.7(2)
	C(1)-C(6)-C(3): 109.4(2)	O(1)-C(7)-N(1): 120.8(2)
	O(1)-C(7)-C(1): 121.1(2)	N(1)-C(7)-C(1): 118.2(2)
3-29a	N(1)-S(1)-C(2): 93.8(1)	C(1)-O(1)-C(2): 111.9(2)
	S(1)-N(1)-C(1): 109.4(2)	O(1)-C(1)-N(1): 118.8(2)
	O(1)-C(1)-C(3): 115.0(2)	N(1)-C(1)-C(3): 126.2(2)
	S(1)-C(2)-O(1): 106.2(2)	S(1)-C(2)-O(2): 130.7(2)
	O(1)-C(2)-O(2): 123.1(2)	C(1)-C(3)-C(4): 109.8(2)
	C(1)-C(3)-C(8): 109.9(2)	C(1)-C(3)-C(9): 110.2(2)
	C(4)-C(3)-C(8): 109.8(2)	C(4)-C(3)-C(9): 108.2(2)
	C(8)-C(3)-C(9): 108.8(2)	C(3)-C(4)-C(5): 110.1(2)
	C(4)-C(5)-C(6): 109.3(2)	C(4)-C(5)-C(11): 109.6(2)
3-28b	N(1)-S(1)-C(1): 93.6(1)	C(1)-O(1)-C(2): 111.7(2)
	S(1)-N(1)-C(2): 109.5(2)	S(1)-C(1)-O(1): 106.4(2)
	S(1)-C(1)-O(2): 131.5(3)	O(1)-C(1)-O(2): 122.1(3)
	O(1)-C(2)-N(1): 118.8(3)	O(1)-C(2)-C(3): 114.1(3)
	N(1)-C(2)-C(3): 127.1(3)	C(2)-C(3)-C(4): 114.1(3)
	C(3)-C(4)-C(5): 112.7(3)	C(4)-C(5)-C(6): 114.6(3)
	C(5)-C(6)-C(6'): 114.1(3)	

Table A2-3 Selected bond Angles (°) for 2-7, 3-27a to 3-47, 4-4c (continued)

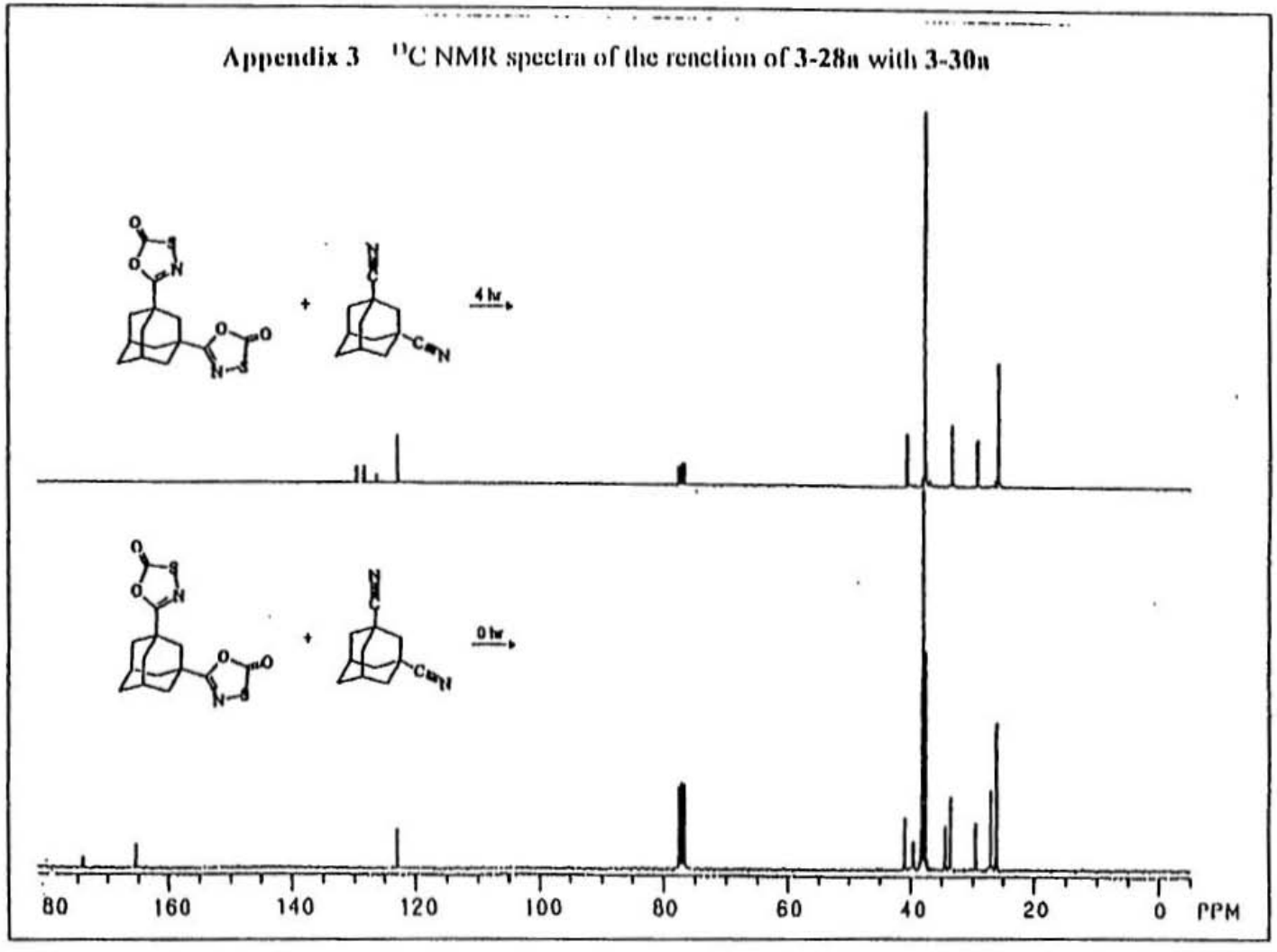
Compound	Bond Angles	
3-31	N(1)-S(1)-C(3): 95.1(3)	N(2)-S(2)-C(6): 94.7(3)
	C(17)-O(1)-C(18): 115.3(6)	S(1)-N(1)-C(1): 110.6(5)
	S(2)-N(2)-C(4): 110.6(5)	N(1)-C(1)-C(2): 115.2(6)
3-31	N(1)-C(1)-C(9): 118.8(6)	C(2)-C(1)-C(9): 126.0(6)
	C(1)-C(2)-C(3): 110.0(6)	C(1)-C(2)-C(17): 128.8(6)
	C(3)-C(2)-C(17): 121.2(6)	S(1)-C(3)-C(2): 109.1(5)
	S(1)-C(3)-C(19): 124.2(5)	C(2)-C(3)-C(19): 126.8(6)
	N(2)-C(4)-C(5): 114.8(6)	N(2)-C(4)-C(7): 119.0(6)
	C(5)-C(4)-C(7): 126.2(6)	C(4)-C(5)-C(6): 111.4(6)
	C(4)-C(5)-C(21): 128.7(6)	C(6)-C(5)-C(21): 119.8(6)
3-32	N(1)-S(1)-C(3): 93.8(3)	C(3)-C(2)-C(14): 124.3(6)
	C(14)-O(2)-C(15): 115.1(5)	S(1)-C(3)-C(2): 110.4(5)
	C(16)-O(4)-C(17): 114.2(6)	S(1)-C(3)-C(16): 118.8(5)
	S(1)-N(1)-C(1): 111.1(5)	C(2)-C(3)-C(16): 130.8(6)
	N(1)-C(1)-C(2): 116.0(6)	C(1)-C(4)-C(5): 109.0(5)
	N(1)-C(1)-C(4): 118.9(6)	C(1)-C(4)-C(9): 109.3(5)
	C(2)-C(1)-C(4): 124.9(6)	C(1)-C(4)-C(10): 112.5(6)
	C(1)-C(2)-C(3): 108.7(6)	C(5)-C(4)-C(9): 107.6(5)
	C(1)-C(2)-C(14): 127.0(6)	C(5)-C(4)-C(10): 108.1(5)
3-41	N(1)-S(1)-C(1): 94.1(2)	O(1)-C(2)-C(3): 114.2(4)
	N(2)-S(2)-C(4): 95.5(2)	N(1)-C(2)-C(3): 126.6(4)
	C(1)-O(1)-C(2): 111.1(3)	C(2)-C(3)-C(4): 122.3(4)
	S(1)-N(1)-C(2): 108.4(3)	C(2)-C(3)-C(5): 126.6(4)
	S(2)-N(2)-C(5): 110.1(3)	C(4)-C(3)-C(5): 110.9(4)
	S(1)-C(1)-O(1): 107.3(3)	S(2)-C(4)-C(3): 108.8(3)
	S(2)-C(1)-O(2): 130.6(4)	N(2)-C(5)-C(3): 114.6(4)
	O(1)-C(1)-O(2): 122.0(4)	N(2)-C(5)-C(6): 118.2(4)
	O(1)-C(2)-N(1): 119.1(4)	C(3)-C(5)-C(6): 127.1(4)
3-42	N(1)-S(1)-C(1): 93.1(2)	O(1)-C(2)-C(3): 115.9(3)
	N(2)-S(2)-C(3): 94.6(2)	N(1)-C(2)-C(3): 124.8(3)
	C(1)-O(1)-C(2): 111.2(3)	S(2)-C(3)-C(2): 121.5(3)
	S(1)-N(1)-C(2): 109.4(2)	S(2)-C(3)-C(4): 108.6(3)
	S(2)-N(2)-C(5): 110.4(2)	C(2)-C(3)-C(4): 129.9(3)
	S(1)-C(1)-O(1): 107.1(3)	C(3)-C(4)-C(5): 111.6(3)
	S(1)-C(1)-O(2): 129.3(3)	N(2)-C(5)-C(4): 114.8(3)

Table A2-3 Selected bond Angles (°) for 2-7, 3-27a to 3-47, 4-4c (continued)

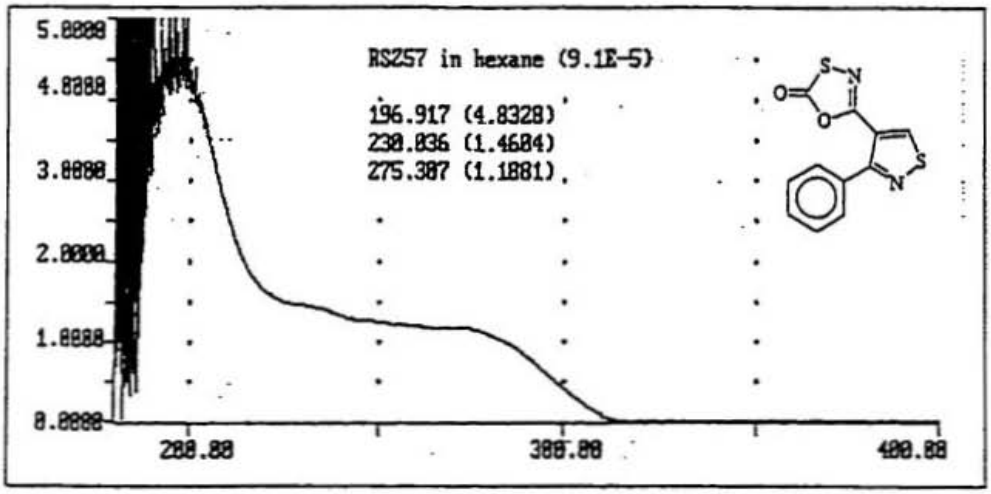
Compound	Bond Angles	
3-42	O(1)-C(1)-O(2): 123.6(4)	N(2)-C(5)-C(6): 119.4(3)
	O(1)-C(2)-N(1): 119.2(3)	C(4)-C(5)-C(6): 125.8(3)
3-43	N(1)-S(1)-C(1): 95.5(1)	C(1)-C(2)-C(3): 110.6(2)
	N(2)-S(2)-C(5): 95.4(1)	C(1)-C(2)-C(13): 124.8(2)
	C(13)-O(1)-C(14): 117.5(2)	C(3)-C(2)-C(13): 124.5(2)
3-43	S(1)-N(1)-C(3): 109.3(2)	N(1)-C(3)-C(2): 115.2(2)
	S(2)-N(2)-C(6): 109.5(2)	N(1)-C(3)-C(4): 118.3(2)
	S(1)-C(1)-C(2): 109.4(2)	C(2)-C(3)-C(4): 126.5(2)
	S(2)-C(5)-C(4): 109.5(2)	C(3)-C(4)-C(5): 122.7(2)
	O(1)-C(13)-O(2): 124.7(2)	C(3)-C(4)-C(6): 127.0(2)
	O(1)-C(13)-C(2): 124.3(2)	C(5)-C(4)-C(6): 110.3(2)
3-46	N(1)-S(1)-C(3): 94.9(1)	C(1)-C(2)-C(13): 121.9(3)
	N(2)-S(2)-C(4): 95.4(1)	S(1)-C(3)-C(2): 110.4(2)
	C(13)-O(2)-C(14): 116.4(3)	S(2)-C(4)-C(1): 117.5(2)
	S(1)-N(1)-C(1): 110.5(2)	S(2)-C(4)-C(6): 107.9(2)
	S(2)-N(2)-C(5): 109.8(2)	C(1)-C(4)-C(6): 134.6(3)
	N(1)-C(1)-C(2): 114.4(3)	N(2)-C(5)-C(6): 114.9(3)
	N(1)-C(1)-C(4): 114.5(3)	C(6)-C(5)-C(7): 125.3(3)
	C(2)-C(1)-C(4): 131.1(3)	C(4)-C(6)-C(5): 111.9(3)
	C(1)-C(2)-C(3): 109.8(3)	C(5)-C(7)-C(8): 121.1(3)
3-47	N(1)-S(1)-C(3): 94.2(4)	C(1)-C(4)-C(6): 129.1(7)
	N(2)-S(2)-C(4): 96.3(4)	S(1)-C(3)-C(2): 109.2(6)
	C(13)-O(2)-C(14): 116.6(6)	S(1)-C(3)-C(13): 121.4(6)
	S(1)-N(1)-C(1): 110.1(5)	S(2)-C(4)-C(6): 107.6(6)
	S(2)-N(2)-C(5): 108.8(6)	S(2)-C(4)-C(1): 123.4(6)
	N(1)-C(1)-C(2): 115.1(7)	N(2)-C(5)-C(6): 115.7(7)
	N(1)-C(1)-C(4): 116.4(7)	C(2)-C(3)-C(13): 129.4(7)
	C(2)-C(1)-C(4): 128.5(7)	C(4)-C(6)-C(5): 111.7(7)
	C(1)-C(2)-C(3): 111.4(7)	O(1)-C(13)-C(3): 125.1(8)
4-4c	N(1)-S(1)-C(1): 93.8(1)	C(2)-C(3)-C(4): 122.1(3)
	C(1)-O(2)-C(2): 111.3(2)	C(2)-C(3)-C(8): 119.7(3)
	S(1)-N(1)-C(2): 109.4(2)	C(4)-C(3)-C(8): 118.2(3)
	S(1)-C(1)-O(1): 131.1(3)	C(3)-C(4)-C(5): 120.3(3)
	S(1)-C(1)-O(2): 106.7(2)	C(4)-C(5)-C(6): 122.5(3)

Table A2-3 Selected bond Angles (°) for 2-7, 3-27a to 3-47, 4-4c (continued)

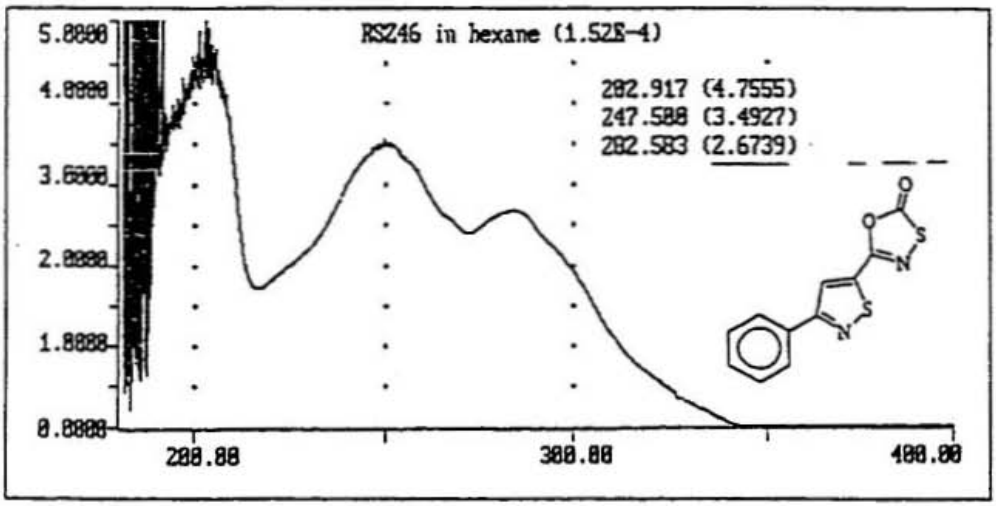
Compound	Bond Angles	
4-4c	O(1)-C(1)-O(2): 122.1(3)	C(5)-C(6)-C(7): 115.9(3)
	O(2)-C(2)-N(1): 118.7(3)	C(5)-C(6)-C(9): 122.2(2)
	O(2)-C(2)-C(3): 116.1(2)	C(7)-C(6)-C(9): 121.9(2)
	N(1)-C(2)-C(3): 125.1(3)	C(6)-C(7)-C(8): 122.2(3)


Appendix 3 ^{13}C NMR spectra of the reaction of 3-28a with 3-30a
4 hr
0 hr
80
160
140
120
100
80
60
40
20
0
PPM

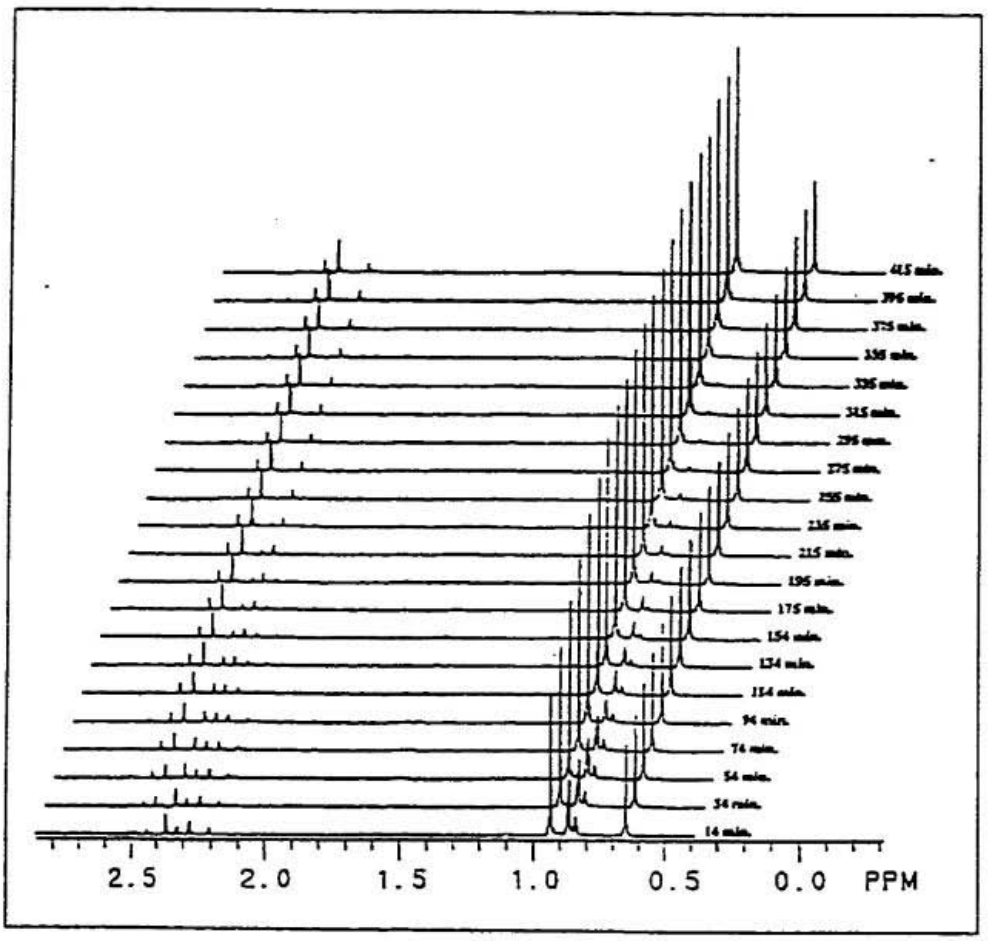
Appendix 4 UV-visible spectrum of 5-(3'-phenyl-isothiazol-4'-yl)-1,3,4-oxathiazol-2-one **3-41**



Appendix 5 UV-visible spectrum of 5-(3'-phenyl-isothiazol-5'-yl)-1,3,4-oxathiazol-2-one **3-42**



Appendix 6 The reaction of $CH_3C(OSiMe_3)=NSiMe_3$ + ClSC(O)Cl in $CDCl_3$ at 25°C monitored by ^1H NMR



Appendix 7 ^{1}H NMR spectra of *N,N*-bis(trimethyl)-*p*-toluenesulfinamide **5-29** in $CDCl_3$ at different temperature (-60°C to 60°C)