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Synthesis and application of thiourea-*S*,*S*-dioxide derivatives

by

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A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry

University of Warwick

Department of Chemistry

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To my parents

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Declaration

The material presented in this thesis is solely based on original research by the author, unless otherwise stated. All published work cited in the text are acknowledged and fully referenced. None of the author's work, detailed in this thesis, has been submitted or published at any other academic institution.

Abstract

The structure and synthesis of *N,N'*-disubstituted thiourea-*S,S*-dioxides were investigated experimentally and computationally. Hydrogen peroxide oxidation of acyclic and cyclic *N,N*'-dialkylthioureas furnished *S,S*-dioxides in agreement with computational predictions. Some *S,S,S*-trioxides were also isolated. An X-ray crystallographic study of *N,N'*-diisopropylthiourea dioxide, first synthesised in this work, verified computational models. The prediction of a stable *N,N'*-diarylthiourea dioxide derivative was supported by successful isolation of the dioxide.

The application of *N,N'*-diisopropylthiourea dioxide as a reducing agent was investigated. Removal of tosyl groups from *N*-tosylaziridines, deprotection of CBz-amines and reduction of nitriles could not be realised. However, aldehydes and ketones were successfully reduced to the respective alcohols in yields comparable with that of thiourea dioxide. Disulfides and *N*-tosylsulfimides were reduced to a higher degree with *N,N'*-diisopropylthiourea dioxide than thiourea dioxide under simple, mild conditions.

The mechanism of decomposition of *N,N'*-diisopropylthiourea dioxide to give radical anions was investigated with *N*-tosylsulfimides and a cyclopropylketone. The study revealed that at high pH, heterolysis of the C-S bond in *N,N'*-diisopropylthiourea dioxide led to the formation of a sulfinate dianion SO_2^{2-}. The dianion was thought to rapidly oxidise to a powerful reducing species, the radical anion $SO_2^{\cdot-}$ and subsequently effect reduction *via* a single-electron transfer pathway. A full mechanism of decomposition and reduction is proposed.

An investigation into the role of thiourea dioxides as *N*-heterocyclic carbene (NHC) synthons was carried out. It was thought that decomposition of ethylenethiourea dioxides, *via* the elimination of sulfur dioxide, would provide an alternative approach to metal NHC complex synthesis. Oxaziridine oxidation of acyclic thioureas, successfully established in this work, was applied to the preparation of ethylenethiourea dioxides. A short study revealed considerable potential for thiourea dioxides as NHC precursors.

Abbreviations

AIMS	Aminoiminomethanesulfinic acid
AM1	Austin model-1
br	broad
B3LYP	DFT functional (developed by Becke, Lee, Yang and Parr)
BOC	*tert*-Butoxycarbonyl
CBS	Complete basis set
CBz	Carboxybenzyl (alternatively abbreviated **Z**)
CI	Chemical ionisation
COSY	Correlated spectroscopy
d	doublet
DBA-DBU	6-(Di-*n*-butylamino)-1,8-diazobicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DFT	Density functional theory
DMAP	4-*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DMDO	Dimethyldioxirane
DNA	Deoxyribonucleic acid
EBDC	Ethylenebisdithiocarbamate
EI	Electron impact
EPR	Electron paramagnetic resonance
ESI	Electrospray ionisation
equiv.	equivalents

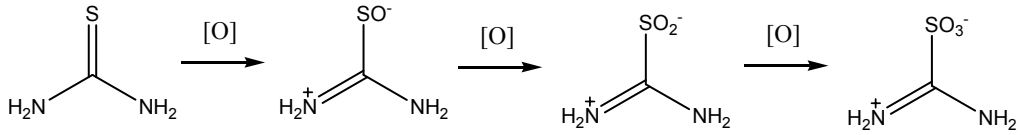
FAB	Fast atom bombardment
FASA	Formamidinesulfinic acid
FMO	Flavin-containing monooxygenase
GC	Gas chromatography
GLC	Gas-liquid chromatography
GCMS	Gas chromatography-Mass spectrometry
GSH	Glutathione
GSSG	Glutathione disulfide
HF	Hartree Fock (*ab initio* method)
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear multiple quantum coherence
HRMS	High resolution mass spectrometry
IEFPCM	Integral equation formalism polarisable continuum model
IR	Infrared
J	coupling constant
LSIMS	Liquid secondary ion mass spectrometry
m	multiplet
MCPBA	*meta*-Chloroperbenzoic acid
Mes	Mesityl or 2,4,6-trimethylphenyl
MP2	Second-order Møller-Plesset (perturbation method)
Mpt	melting point
MS	Mass spectrometry
MTBE	Methyl *tert*-butyl ether
NHC	*N*-Heterocyclic carbene

NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
PDC	Pyridinium dichromate
PSO	*N*-Phenylsulfonyloxaziridine
R_f	retention factor
R_t	retention time
RT	room temperature
s	singlet
SET	Single electron transfer
t	triplet
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMDO	Methyl(trifluoromethyl)dioxirane
TMS	Tetramethylsilane
TPAP	Tetra-*n*-propylammonium perruthenate
Ts	Tosyl or *para*-toluenesulfonyl
UV	Ultraviolet

Chapter 1. Introduction

1.1 Preface

Thiourea-*S,S*-dioxide **3**, also known as formamidinesulfinic acid (FASA) or aminoiminomethanesulfinic acid (AIMS), is produced *via* the oxidation of thiourea **1**.[1, 2] Thiourea-*S*-monoxide **2** and thiourea-*S,S,S*-trioxide **4** are referred to as the sulfenic- and sulfonic-acid counterparts of **3**, respectively, and are outlined in Scheme 1.

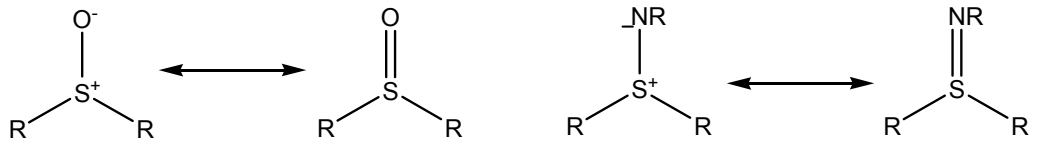


1, thiourea **2**, thiourea-*S*-monoxide **3**, thiourea-*S,S*-dioxide **4**, thiourea-*S,S,S*-trioxide

Scheme 1. Oxidation states of thiourea

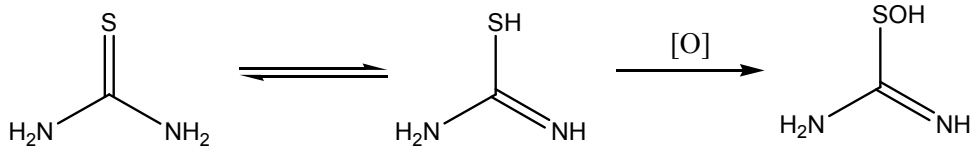
The various oxidation states of thiourea (and that of organosulfur compounds in general) gives rise to a rich and diverse chemistry which is often compounded by its apparent complexity. In this thesis, thiourea-*S,S*-dioxide will be referred to as 'dioxide' and we shall rarely make use of 'sulfinic acid' nomenclature. Similarly, thiourea-*S*-monoxide and thiourea-*S,S,S*-trioxide will also be referred to as monoxide and trioxide, respectively.

It is known that π-bonding between sulfur and other smaller atoms *e.g.* carbon, nitrogen and oxygen, is weak. For example, theoretical studies have shown sulfimide[3-5] and sulfoxide[6] sulfur-heteroatom bond lengths and orders are intermediate of single and double bonds. Sulfur oxides show a high degree of ionicity, as shown by second-order Møller-Plesset MP2 level theoretical studies.[7] In this thesis, compounds which contain such bonds will be represented as ylids.



Scheme 2. Ylid structures of sulfoxides and sulfimides

Similarly, it is argued that thioureas undergo thione-thiol tautomerism[8] to isothioureas (Scheme 3), which is thought to explain some reaction pathways such as sulfenic acid formation.[9]



Scheme 3. Oxidation of isothiourea

However this has yet to be established substantially. Thiourea[10] possesses a C-S bond length of 1.716 Å which is shorter than the covalent radii of a C-S single bond 1.81 Å.[11] The difference in Pauling electronegativity between carbon 2.55 and sulfur 2.58 is small.[11] Consequently, polarisation of the thiourea CS bond is less pronounced when compared to the SN bonds in sulfimides and the SO bonds in sulfoxides. Therefore, for the purposes of this thesis, thioureas will be represented with C=S double bonds.

What follows in this introduction is an overview of the oxidation states of sulfur compounds. The role of thiourea oxides in biological systems is then outlined, followed by considerations to the structure and oxidation pathways of thiourea. Finally, X-ray crystallographic and computational structural studies, and synthetic applications of the oxides of thiourea are presented.

The results and discussion are then presented in four chapters. Chapter 2 deals with the synthesis and characterisation of *N,N'*-disubstituted thiourea dioxide derivatives, which

includes X-ray and computational studies. The next chapter outlines an investigation into the synthetic utility of disubstituted thiourea dioxides as applied to a series of nitrogen, oxygen and sulfur-containing substrates. The fourth chapter presents experimental evidence to suggest potential decomposition and reduction mechanisms of thiourea dioxides. The final discussion concentrates on studies towards a new application centring on the use of thiourea dioxides as carbene precursors.

1.2 Oxidation of sulfur compounds

Sulfur possesses a wide oxidation range of -2 to +6.[12] Sulfur compounds often exist as complex structures, where the valency of sulfur is greater than two. This is in contrast to oxygen, where the valency is fixed at two. In part, this means that divalent sulfur compounds can be converted to species in which the central sulfur atom accommodates more than four pairs of electrons. For example hydrogen sulfide H_2S, S = -2, can be oxidised to sulfate SO_4^{2-}, S = +6. The sulfur atom in sulfates accommodates up to six electron pairs. The expansion of the valence shell violates the Lewis octet rule.[13]

The expansion of the valence shell on sulfur was thought to arise from the promotion of bonding electrons into the low-lying empty d-orbitals. However, more recent *ab initio* calculations revealed that d-orbital contributions to bonding were insignificant compared with s- and p-contributions.[14] Mixon and Cioslowski discovered that bonding in systems, such as SO_2, SO_3 and SO_4^{2-}, are highly polarized and considerably ionic in nature.[7] The SO bonding electrons are thought to localise to the more electronegative oxygen and lead to a reduction of electron density in the valence shell on sulfur. This apparently leads to an electronic configuration at the sulfur centre which does not violate the octet rule. Theoretical chemists continue to debate the topic.[15]

The definition of hypervalency is questioned by some authors.[14] In view of this, Gillespie and Robinson proposed that it is more useful to recognize that a duet rule (one electron pair) applies to the period 1 elements, an octet rule (four pairs) to the period 2 elements

and a duodecet rule (six pairs) to the period 3 and 4 elements.[16] Overall, the ionicity of sulfur compounds above a valency of two is now considered a more accurate description, compared with d-orbital contributions, of the bonding.

Confusion in the literature is occasionally encountered with regard to the assignment of the oxidation states of organosulfur compounds. The examples, listed in Table 1, are assigned based on the difference of electronegativities between sulfur and the atom bonded to sulfur. Sulfur is more electronegative than carbon in, for example, dimethyl sulfide Me_2S and therefore possesses a formal oxidation state of -2. Sulfur is less electronegative than oxygen in sulfate SO_4^{2-} and is therefore assigned a formal oxidation state of +6. Table 1 lists the intermediate oxidation states of sulfur (boldface) with some examples, including compounds with more than one sulfur centre *e.g.* thiosulfinates RS(O)SR and key intermediate species[†] discussed in this thesis.

Oxidation state of S	Examples		
-2	Thiol/mercaptan R**S**H	Sulfide R_2**S**	Thioketone R_2C=**S**
-1	Thiosulfinate R**S**S(O)R	Disulfide R**S**SR	Thiosulfonate R**S**SO_2R
0	Elemental sulfur $\mathbf{S}_8$	Sulfenic acid R**S**OH	Sulfoxide R**S**(O)R
+1	Thiosulfinate RS**S**(O)R		
+2	[†a]Sulfinate $\mathbf{S}O_2^{2-}$	Sulfinic acid R**S**O_2H	Sulfone R**S**O_2R
+3	[†]radical anion $\mathbf{S}O_2^{\cdot-}$	[†b]Dithionite $\mathbf{S}_2O_4^{2-}$	Thiosulfonate RS**S**O_2R
+4	Sulfur dioxide $\mathbf{S}O_2$	Sulfonic acid R**S**O_3H	Sulfite $\mathbf{S}O_3^{2-}$
+5	Thiosulfate RS**S**O_3^-	Dithionate $\mathbf{S}_2O_6^{2-}$	
+6	Sulfate $\mathbf{S}O_4^{2-}$		

a: SO_2^{2-} is also referred to as sulfoxylate by some authors, derived from sulfoxylic acid H_2SO_2

b: Dithionite is also referred to as hydrosulfite

Table 1. Examples of sulfur compounds

The stability of organosulfur compounds is not reflected in the oxidation state alone but is also dependent on neighbouring atoms. For example, sulfenic acids S = 0, readily oxidise[17] or dimerise[17-19] and are less stable than elemental sulfur, also at the zero oxidation state.

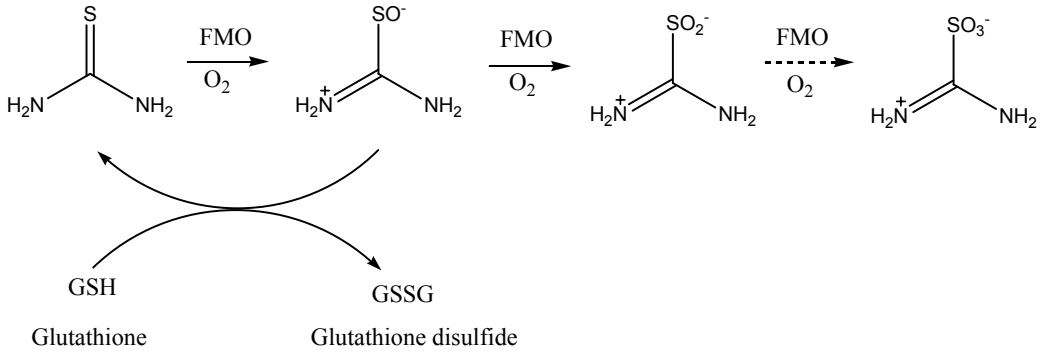
Vowels are often used in an attempt to unambiguously refer to the oxidation states of sulfur.[12] For example, sulf**e**nic acid with S = 0 oxidation state, sulf**i**nic S = +2 oxidation state and sulf**o**nic S = +4 oxidation state. The naming of other compounds, listed in Table 1, does not always follow suit and are easily misinterpreted. It is for this reason that the title compounds of this thesis will be referred to, where possible, on the number of oxygen atoms attached to sulfur *e.g.* monoxides, dioxides and trioxides.

Perhaps the most significant consequence of the variable oxidation states of sulfur lies in the study of biological systems where sulfur participates in redox reactions. This forms the next part of the introduction and will be restricted to compounds which are of interest in this thesis: derivatives of thiourea.

1.3 Thiourea oxides in biological systems

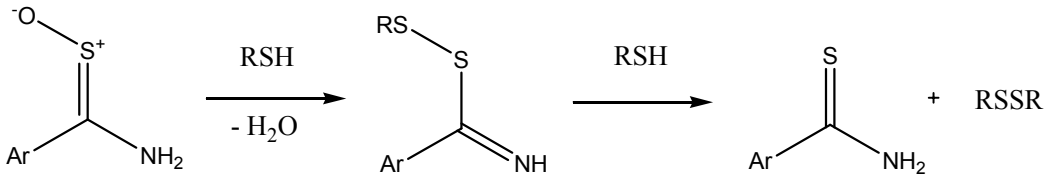
The mechanisms underlying the biological effects of thiourea, the simplest of thiocarbamides, are not fully understood. The majority of previous thiourea pharmacological studies were carried out on α-naphthylthiourea which is known to be a pulmonary toxin, more especially for rats than for other species.[20] Paraquat is a herbicide known to induce superoxide radical $O_2^{\cdot-}$ formation in human cells. Thiourea was found to actively scavenge for superoxide radicals and lower paraquat intoxication.[21]

It is known that the oxides of thiourea play a major role in the metabolic pathways described below. The capacity of thiourea to readily oxidise to the monoxide *in vivo* results in the depletion of vital endogenous antioxidants *e.g.* glutathione GSH, and subsequent deprotection of cellular structures from oxidant attack. Pharmacological studies have shown that the oxidation of sulfur in thiourea *in vivo* is most probably catalysed by flavin-containing monooxygenase (FMO),[9, 22] an important mammalian enzyme which oxidises xenobiotic substances. The major products of oxidation are thiourea-monoxide and -dioxide, although in some cases thiourea trioxide has been detected. The formation of the trioxide is much slower and not thought to be catalysed by FMO.[23]



Scheme 4. Oxidation of thiourea *in vivo*

Thiourea monoxide is thought to be reduced back to thiourea by intracellular non-protein thiols, notably GSH, and this is supported by the persistent depletion of intracellular GSH.[23, 24] Glutathione depletion is characterised by the formation of glutathione disulfide GSSG. The reduction of thiourea monoxide *in vivo* is analogous to the reduction of thiobenzamide-*S*-oxides by thiols (Scheme 5). A conclusion from the study[25] suggests that the toxicity of thioamides is mainly due to the formation of thiobenzamide-*S*-oxides.

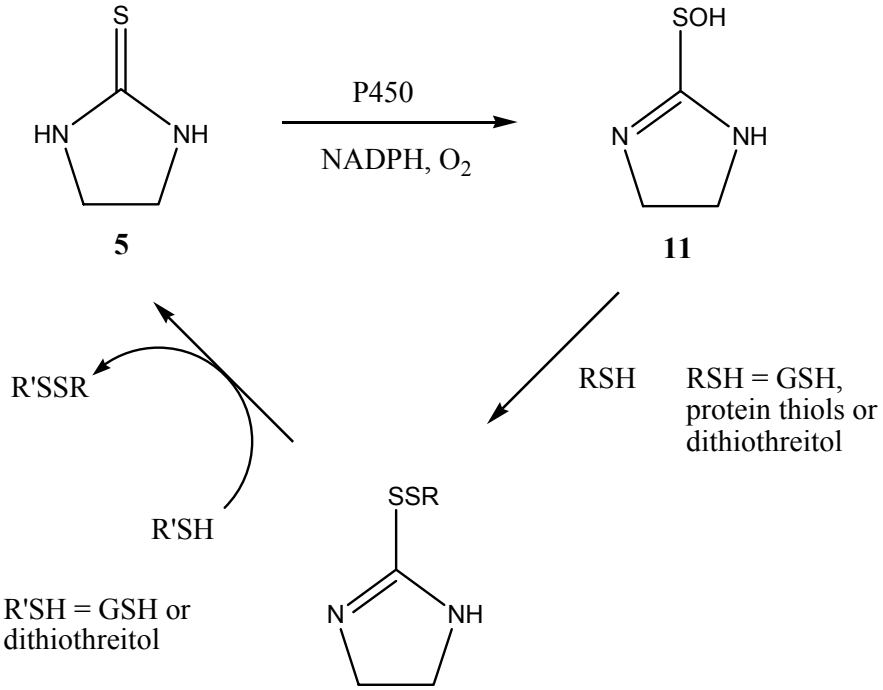


Scheme 5. Reduction of thiobenzamide-*S*-oxides

Hardwick and co-workers found that a controlled increase in GSH levels led to a reduction in lung toxicity of α-naphthylthiourea *in vivo*.[26]

Vermeulen and co-workers compared the cytotoxicity of a series of substituted thioureas, including α-naphthylthiourea, in order to understand the mechanisms of cytotoxicity and the structure-toxicity relationships. They found that *N*-phenylthiourea and α-naphthylthiourea resulted in the highest GSH depletion. However, other *N*-alkylthioureas gave less.[24]

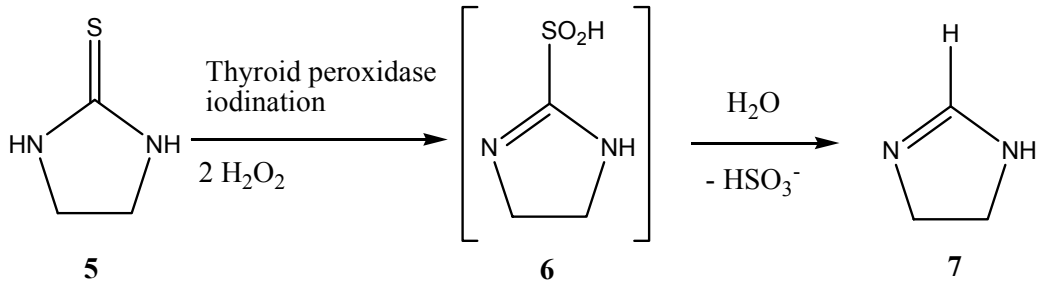
Alternative mechanisms which explain the pharmacology of thioureas have centred on cytochrome P450, found in hepatocytes. Decker and Doerge found that there was significant contribution of FMO and P450 mediated oxidation of ethylenethiourea **5** in rats.[27] Ethylenethiourea, bound to P450, was found to inactivate P450 enzymes through the formation of ethylenethiourea monoxide **11**. The addition of GSH or other thiol reagents, for example dithiothreitol, was thought to isolate the monoxide and release P450. The resultant disulfide (Scheme 6) was not sequestered from the protein and readily reacts with more GSH or dithiothreitol to regenerate ethylenethiourea.



Scheme 6. Effect of added thiols to the hepatic P450 mediated metabolism of ethylenethiourea[27]

Marshall and Singh investigated the potential use of hypochlorite at high pH to inactivate ethylenethiourea through oxidation, with particular reference to the formation of ethylenethiourea from ethylenebisdithiocarbamate EBDC fungicide residues. They studied the oxidation of ethylenethiourea, with a view to inactivating the potentially harmful residues in food, prior to human consumption.[28]

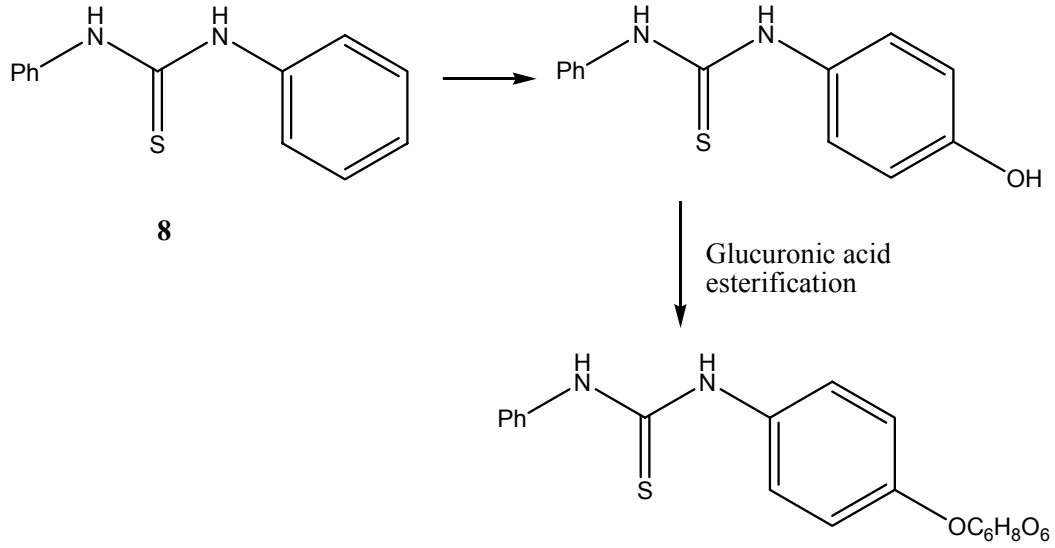
Deorge and Takazawa published mechanistic studies on the inhibition of thyroid peroxidase, which catalyses the iodination and coupling of tyrosine residues in the synthesis of thyroid hormones, with ethylenethiourea.[29] They suggest that ethylenethiourea **5**, in the presence of an enzyme-generated iodination intermediate, was oxidised to ethylenethiourea dioxide **6** and hydrolytically decomposed to 2-imidazoline **7** and bisulfite (Scheme 7).



5 **6** **7**

Scheme 7. Mechanism of ethylenethiourea metabolism by thyroid peroxidase[29]

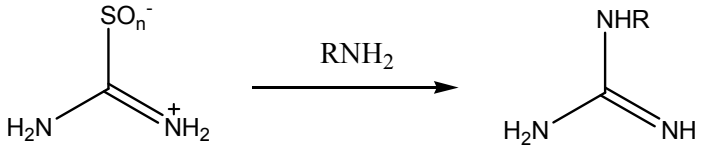
The metabolism of thiourea was also found to occur *via* pathways which did not involve oxidation of the sulfur atom. Smith and Willams found, in rabbit species, that derivatives of *N,N'*-diphenylthiourea do not undergo desulfurisation *in vivo*.[30] The products were excreted mainly as the *para*-hydroxy metabolites with the thione group intact (Scheme 8). This is then followed by esterification with glucuronic acid to complete the detoxification mechanism. *N,N'*-Diphenylthiourea **8** was therefore considered to be non-toxic.[30]



Scheme 8. Detoxification of *N,N'*-diphenylthiourea

In contrast, mono-substituted thioureas, for example *N*-phenylthiourea, were found to desulfurise *in vivo* in rats and rabbits.[31] The study was carried out using radio-labelled *N*-phenylthiourea. *N*-Phenyl(^{35}S)thiourea was recovered as ^{35}S-inorganic sulfate. It was therefore suggested that either *N*-phenylthiourea is toxic *per se* or that toxicity is related to the desulfurisation through the release of hydrogen sulfide. In a later work, Williams and Smith had found that aqueous solutions of hydrogen sulfide administered intravenously into rats were toxic. However, they could not confirm if hydrogen sulfide was formed from the desulfurisation of *N*-phenylthiourea.[32]

Alternative proposals regarding the pharmacology of thiourea derivatives have been published. The oxides of thiourea are reactive electrophiles and have been applied synthetically to the formation of guanidines with amines.[1]



n = 2 or 3

Scheme 9. Guanylation reactions of amines with thiourea-dioxide (n = 2) and -trioxide (n = 3)

The observation that thiourea dioxide induces gene mutations in some cell systems suggests that it may be the reactive metabolite responsible for DNA binding, possibly *via* stable adduct formation between the resultant guanidine moiety and the bases of DNA.[9] Higher doses lead to increased mutation frequency.

Miller and co-workers studied the substitution reactions of the derivatives of phenylthiourea trioxide with glycine and cited steric reasons to explain the difference in reactivity. The toxicity of thiourea derivatives was linked to the rate of substitution of the corresponding trioxides.[1, 33] Thiourea dioxides are poorer electrophiles to substitution *e.g.* guanidine formation, than thiourea trioxide.

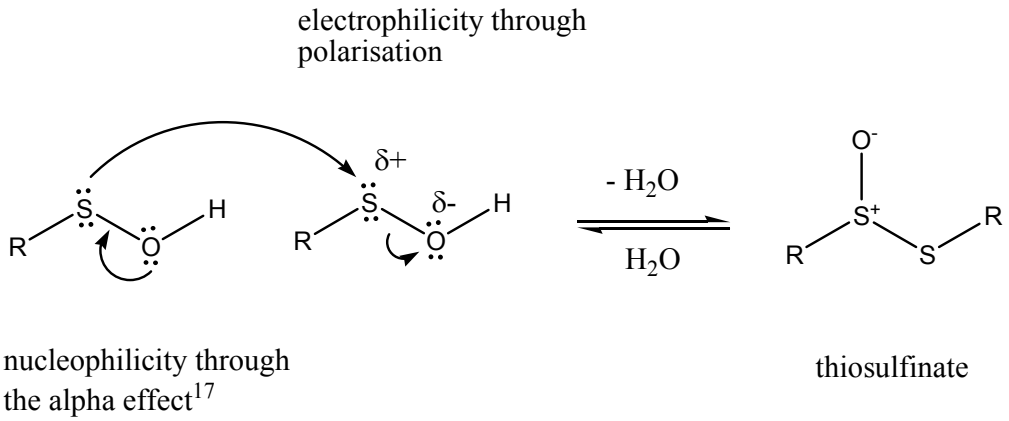
Simoyi recently published mechanistic studies on the decomposition of thiourea dioxides and proposed that thiourea pharmacology is also related to the generation of harmful superoxide $O_2^{\cdot-}$, hydroxyl radical $OH^{\cdot}$ and peroxide O_2^{2-} species.[34] *N,N'*-Dimethylthiourea, a precursor to *N,N'*-dimethylthiourea dioxide, is known to be very toxic in rats. According to Simoyi, *N,N'*-dimethylthiourea dioxide decomposed, to yield the harmful species, at a faster rate than thiourea dioxide or *N*-methylthiourea dioxide.[35]

The mechanisms proposed in the literature which describe the formation of thiourea dioxides and their decomposition pathways, are discussed in 1.4.2.

1.4 Structure, synthesis and properties of the oxides of thiourea

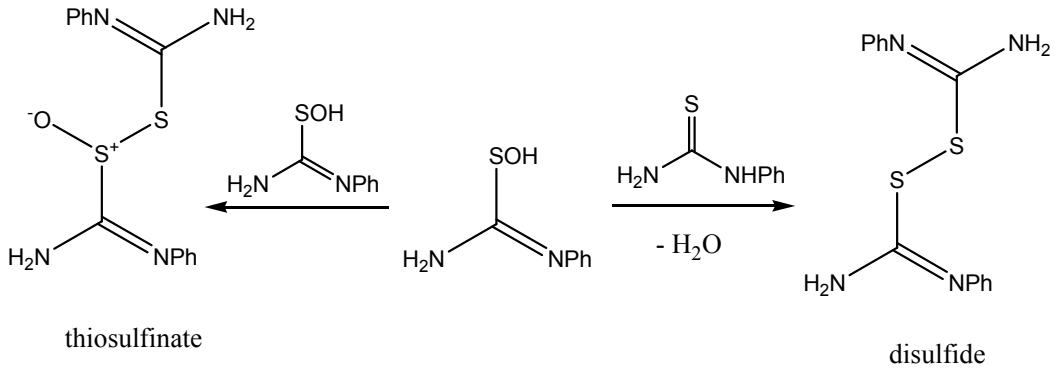
1.4.1 Thiourea monoxide

Thiourea monoxide contains sulfur at oxidation state 0 and is thought to be the precursor to the corresponding dioxide. Thiourea monoxides, like sulfenic acids, contain adjacent S-O non-bonded electron pairs. The sulfur atom is also thought to be polarised by the neighbouring oxygen atom. The combination of adjacent non-bonded electron pairs and partial positive charge on the sulfur atom is thought to account for the nucleophilic and electrophilic reactivity of sulfenic acids.[12, 17]



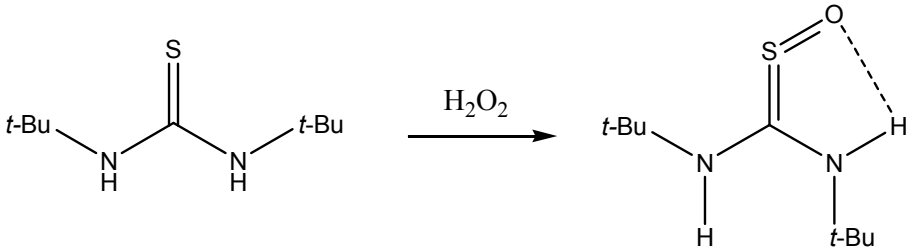
Scheme 10. Nucleophilic and electrophilic reactivity of *S*-monoxides

Thiourea monoxide **2** has not been isolated and is thought to be very unstable.[36] For example, the reactivity of thiourea monoxides was used to explain the formation of thiosulfinate intermediates through dimerisation.[37] The corresponding disulfides were also detected from the reaction of *N*-phenylthiourea monoxide with *N*-phenylthiourea. Both reaction pathways are outlined in Scheme 11.[37]



Scheme 11. Thiosulfinate intermediates and disulfides from thiourea monoxides[37]

Walter and Randau reported the isolation of a series of thiourea monoxide derivatives with bulky groups *e.g. tert*-butyl, *tert*-amyl and 2,6-dimethylphenyl, to name a few.[36] IR spectroscopy revealed a strong peak corresponding to the S=O stretching at 850–905 cm^{-1}. The authors postulated that the compounds adopt a sulfine structure (Scheme 12). They speculated that at -25 ºC, intramolecular hydrogen bonding was evident as judged by the appearance of non-equivalent NMR spectroscopic signals.



1 set of *t*-Bu NMR peaks 2 sets of *t*-Bu NMR peaks

Scheme 12. *N,N'*-Di-*tert*-butylthiourea monoxide[36]

The monoxides isolated by Walter and Randau were found to decompose readily if stored above -20 ºC.

Recently, Williams and co-workers supplied MS data to identify the complex fragmentation pathways of thiourea monoxides, formed from the oxidation of thiourea with human FMO. α-Naphthylthiourea- and *N*-phenylthiourea-monoxide were

investigated. The monoxides were the major metabolite as a result of thiourea administration and bound to GSH or protein cysteine residues.

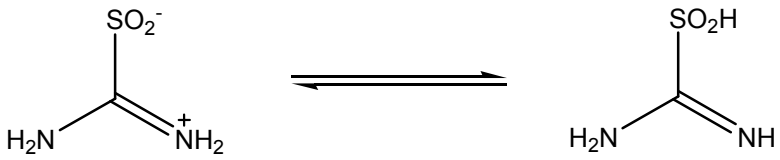
1.4.2 Thiourea dioxide

Thiourea dioxide contains sulfur at the oxidation state +2 and is thought to be the precursor to thiourea trioxide.

1.4.2.1 X-ray crystallographic studies of thiourea dioxides

Thiourea dioxide **3** is commercially available and was first synthesised by Barnett in 1910 *via* oxidation of thiourea with hydrogen peroxide.[2] The structure of thiourea dioxide has been studied both from X-ray crystallographic and computational methods.

Thiourea dioxide is thought to adopt a zwitterionic structure in the solid state.[38] Tautomerism to the neutral form was investigated.



Scheme 13. Tautomerisation of thiourea dioxide

Makarov and Eldik observed the splitting of a singlet ^{1}H NMR signal into a doublet over time. This was explained by the decrease in symmetry along the C-S bond followed by an intermediate exchange between two magnetically non-equivalent nitrogen nuclei.[39] Makarov and Kudrik carried out semi-empirical calculations to show that the neutral form is more stable in aqueous solution than the zwitterion.[40] The decrease in pH was also thought to be indicative of the tautomerisation to the neutral form.[39] In addition, gas phase *ab initio* and density functional theory DFT calculations revealed that the zwitterionic form is less stable than the neutral form. This was demonstrated by the predicted longer C-S bond in the zwitterionic form compared with the neutral form.[41] To our knowledge, there are no analogous computational studies that examine the neutral form of the dioxide in non-aqueous solvents.

The X-ray crystal structure of thiourea dioxide **3** has been deduced several times, initially by Sullivan and Hargreaves[38] in 1961 and then by other groups.[42-45] In 2003, Wang and Lee carried out a combined experimental and theoretical study of thiourea dioxide.[45]

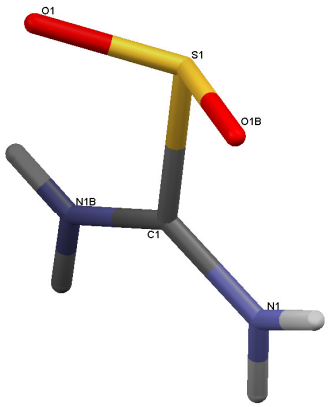
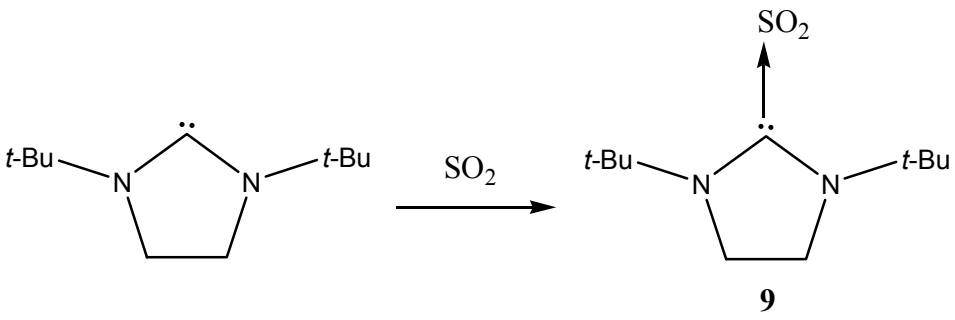


Figure 1. X-ray crystal structure[38] of thiourea dioxide 3

The key observations from the most recent X-ray crystallographic studies are summarized as follows. Thiourea dioxide possesses an unusually long C-S bond[45] of 1.8592 Å (*ab initio* calculated bond order of 0.850)[42] which is significantly longer than thiourea[10] 1.716 Å. There is also extensive intermolecular hydrogen bonding which is thought to account for the high dipole moment[45] of 16.3 D and crystal packing[42] of 1.70 g cm^{-3}. The amidine moiety was found to be planar. The C-N bonds of 1.3096 Å are thought to be shorter than normal C-N single bonds. The terminal $-SO_2^-$ sulfinate group is not in the plane of the amidine moiety and was found to have S-O bonds of 1.4997 Å. The O-Ŝ-O and N-Ĉ-N bond angles are 111.7 º and 124.5 º, respectively.[38] The sulfur lone pair is thought to reside at the apex of the pyramidal sulfinate geometry. The ^{13}C NMR signal in water of thiourea dioxide, at 179.8 ppm, is upfield from thiourea at 184.5 ppm.[46] These data are summarized in comparison with two derivatives in Table 2.

Denk and co-workers obtained an X-ray crystal structure of a substituted thiourea dioxide.[47] They isolated *N,N'*-di-*tert*-butylethylenethiourea-*S,S*-dioxide **9** from the

reaction of the respective carbene with sulfur dioxide (Scheme 14). Their computational work is discussed in more detail later.



9

Scheme 14. Synthesis of *N,N'*-di-*tert*-butylethylenethiourea dioxide[47]

The X-ray crystal structure revealed comparable structural properties to thiourea dioxide. Denk found that the dioxide derivative **9** has a C-S bond of 2.030 Å, longer than thiourea dioxide **3** at 1.8592 Å. Other X-ray crystallographic data, which is comparable with the physical data of the parent dioxide **3**, are listed in Table 2.

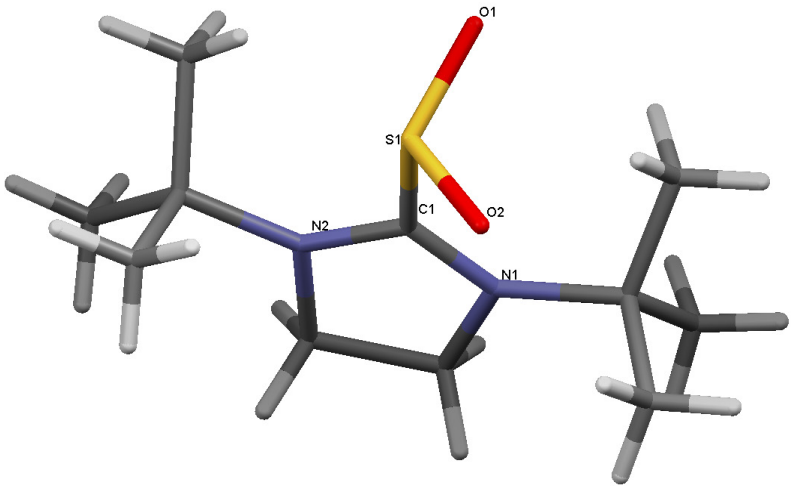


Figure 2. X-ray crystal structure[47] of *N,N'*-di-*tert*-butylethylenethiourea dioxide 9

The most recent X-ray crystal structure of a thiourea dioxide derivative **10**, first synthesised by Repine,[48] was submitted by Simoyi and co-workers.[49]

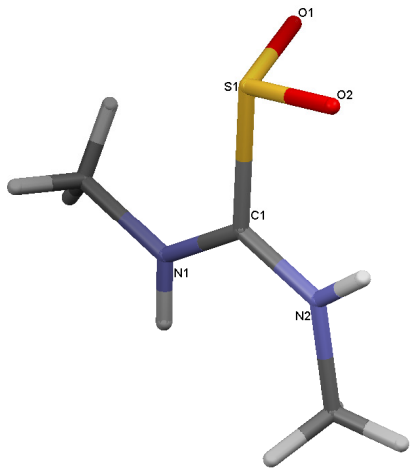


Figure 3. X-ray crystal structure[49] of *N,N'*-dimethylthiourea dioxide 10

The geometry of the sulfinate group is pyramidal and adjacent to a planar amidine moiety. The C-S at 1.880 Å is longer than thiourea dioxide at 1.8592 Å. Repine did not report ^{13}C NMR values for the dioxide but did mention the appearance of three distinct ^{13}C signals. NMR spectroscopic data of **10** was not supplied in Simoyi's publication.[49] The ^{13}C NMR pattern was explained by Repine to be due to hindered rotation about the C-N bond,[48] which is in agreement with Simoyi's X-ray crystallographic data. Key bond lengths and angles of *N,N'*-dimethylthiourea dioxide are listed in Table 2 and compared with the data of thiourea dioxide **3** and Denk's carbene.SO_2 adduct **9**.

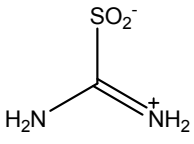
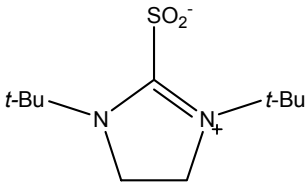
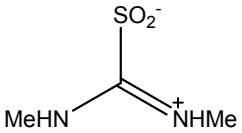
			
	3	**9**	**10**
C-S /Å	1.8592	2.030	1.880
S-O /Å	1.4997	1.4685/1.4693	1.4761/1.4786
amidine C-N /Å	1.3096	1.329/1.339	1.303/1.304
N-Ĉ-N /º	124.5	111.61	123.63
O-Ŝ-O /º	111.7	113.09	112.27
CS ^{13}C /ppm	179.8 (water)	231 (d_6-benzene)	Not supplied
Lit. reference	42, 46-49	51	53

Table 2. Literature thiourea dioxide derivatives

1.4.2.2 Computational studies of thiourea dioxides

The monomer of thiourea dioxide has been studied computationally at Hartree Fock HF,[42] DFT[45, 50] and semi-empirical Austin Model-1 AM1 levels.[40] The calculations indicated that both the carbon and sulfur centres are electrophilic.[42] The pyramidal sulfinate group and planar amidine moiety are faithfully reproduced from X-ray crystallographic studies. More recent DFT calculations revealed the occurrence of intramolecular hydrogen bonding between NH and O. This is in contrast to the observations from X-ray structures, where intramolecular hydrogen bonding in thiourea dioxide was not thought to take place.[45]

Denk and co-workers proposed that thiourea dioxides are carbene-sulfur dioxide Lewis acid-base adducts (Figure 4). With the aid of expensive, high-level Complete Basis Set CBS-Q computational methods, they predicted that thiourea dioxides have C-S bond dissociation energies which are commonly observed for Lewis acid-base adducts. The examples, shown in Figure 4, were found to have C-S dissociation energies in the range 3.30–20.09 kcal mol^{-1}.[47]

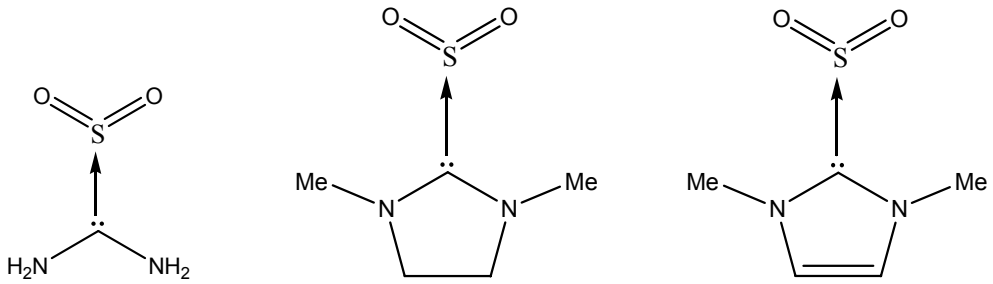
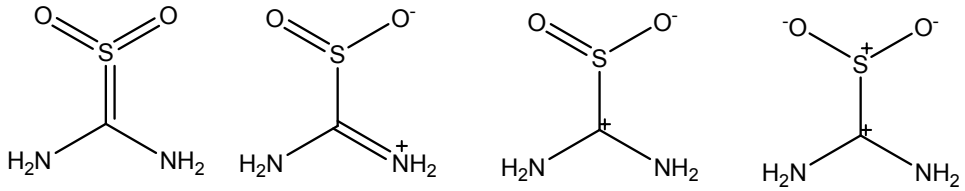


Figure 4. Thiourea dioxides as a Lewis acid-base carbene.SO_2 adduct[47]

Bond order predictions in 1996 speculated that a possible structure for thiourea dioxide is a combination of III and IV (Scheme 15).[42]



Scheme 15. Canonical forms[42] I - IV of thiourea dioxide 3

The existence of sulfene[51, 52] I type structures, considered by some authors,[53, 54] was challenged.[47] From published work, sulfenes are planar in geometry[55, 56] and described as distorted SO_3 units.[57] The X-ray crystallographic studies revealed a pyramidal sulfur centre as shown in Figure 1. The C-S bond was also too long for a double bond. These factors make the contribution of the sulfene smaller than the zwitterionic (II-IV) or neutral forms (Scheme 13).[38]

In 2007, DFT calculations were carried out on multiple thiourea dioxide units, in contrast to the monomer outlined previously.[50] The authors demonstrated good agreement between, for example, C-S bond length, with differences < 0.016 Å between X-ray crystallographic data and a range of DFT methods investigated. Intermolecular hydrogen bonding was predicted from the calculations although intramolecular hydrogen bonding was not.

1.4.2.3 Synthesis of thiourea dioxides

As already mentioned, thiourea dioxide is usually isolated from the hydrogen peroxide oxidation of thiourea.[1, 53] Alternatively, peracetic acid is also used.[53] The reactions are commonly performed below room temperature and in conjunction with a molybdate catalyst.[1, 58-60] It is known that the disproportionation of hydrogen peroxide to water and singlet molecular oxygen is kinetically controlled and is extremely slow at room temperature.[61]

Scheme 16. Disproportionation of hydrogen peroxide

The addition of molybdate MoO_4^{2-} catalysts in hydrogen peroxide solutions gives rise to the formation of yellow diperoxo MoO_6^{2-} and red-brown tetraperoxo MoO_8^{2-} species, which rapidly decompose to MoO_4^{2-} with concomitant release of $^1O_2$.[62-64] In this thesis, oxidising conditions which involve hydrogen peroxide in conjunction with a molybdate catalyst will be referred to as 'catalytic conditions'. Similarly, oxidising conditions with hydrogen peroxide without a molybdate catalyst will be referred to as 'non-catalytic conditions'.

In 1969, Walter and Randau isolated a series of *N*-(2,6-dialkylphenyl)thiourea dioxides (Figure 5) using peracetic acid in methanol at -18 ºC and hydrogen peroxide in ethanol at 0-5 ºC for *ca.* 30 minutes.[53]

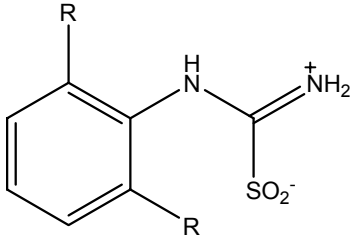


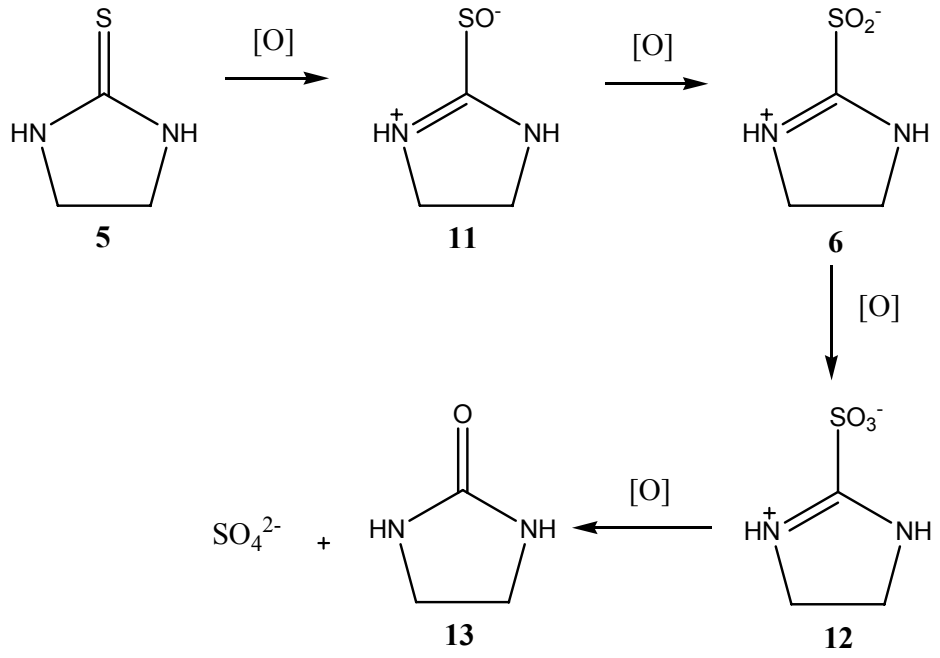
Figure 5. Monosubstituted thiourea dioxides[53]

A series of smaller *N*-alkylthiourea dioxides *e.g.* methyl, *n*-propyl and *sec*-butyl, were isolated using hydrogen peroxide in methanol after 15-30 minutes. *N,N'*-Dicyclohexylthiourea dioxide and *N,N'*-di-*sec*-butylthiourea dioxide were also isolated using hydrogen peroxide or peracetic acid as oxidants. No molybdate catalysts were employed. Walter also identified the terminal sulfinate $-SO_2^-$ stretching modes of the dioxide derivatives at 1020-1005 cm^{-1} (symmetric) and 1099-1080 cm^{-1} (asymmetric).[53]

Yarovenko and Lastovskii published oxidation procedures for alkyl and aryl-substituted thioureas using either hydrogen peroxide with sodium molybdate, ammonium molybdate or with no catalyst at all. They recorded yields of 20-65%, at temperatures of 0-15 ºC and one example at 50 ºC.[59]

In 1972, De Filippo and co-workers isolated thiourea dioxide from thiourea, along with a series of *N,N'*-diaryl derivatives, using an excess of hydrogen peroxide with sodium molybdate at 0-6 ºC. They also isolated sodium salts of the *S,S*-dioxides through treatment of the free sulfinic acid with sodium methoxide.[58]

Marshall and Singh investigated the oxidation of ethylenethiourea **5** with hypochlorite and hydrogen peroxide.[28] They did not successfully isolate the corresponding dioxide **6**. They proposed a pathway to describe the formation of the corresponding monoxide **11**, dioxide **6**, trioxide **12** and imidazolidin-2-one **13**.



Scheme 17. Sodium hypochlorite mediated oxidation of ethylenethiourea[28]

Hypochlorite was thought to oxidise ethylenethiourea through to the corresponding urea **13**. Hydrogen peroxide oxidation stopped at the trioxide stage and was ineffective at oxidising the trioxide to the urea. Further efforts by Marshall[65] and Casida,[66] towards the isolation of ethylenethiourea dioxide using hydrogen peroxide, were unsuccessful.

Alternative oxidation conditions were developed by Shenck and Wirth.[67] They investigated the oxidation of thiourea and *n*-allyl derivatives with singlet oxygen *via* dye-sensitised molecular oxygen.[68] Later, Crank and Mursyidi developed the same procedure and applied it to the oxidation of a series of mono- and di-substituted alkyl and aryl thioureas. However, Crank and Mursyidi could not isolate the corresponding dioxides and instead obtained mixtures with concomitant evolution of sulfur dioxide gas.[69]

In 1987, Bischoff published her thesis, which focused on the synthesis and reactivity of *N*-mono- and *N,N'*-disubstituted thiourea-*S*-oxides.[1] Bischoff isolated *N*-phenylthiourea dioxide using molybdate catalysed oxidation of *N*-phenylthiourea with hydrogen peroxide at a temperature below -4 ºC. However, attempts to isolate *N,N'*-diphenylthiourea

dioxide under the same conditions were unsuccessful. Bischoff also concluded that some of the literature regarding the synthesis of thiourea dioxide derivatives, published at the time, was in error.

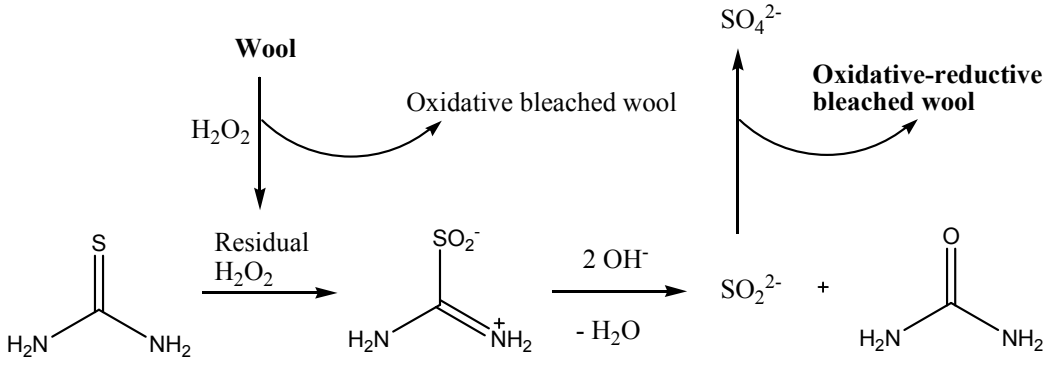
Repine and co-workers published the synthesis of *N,N'*-dimethylthiourea dioxide, known to form *in vivo* from oxidation of *N,N'*-dimethylthiourea.[48] The authors described the hydrogen peroxide oxidation of the parent thiourea at ice-bath temperatures, followed by purification, to give the dioxide. No yields were supplied in their report. The compound was characterised from IR and elemental analyses. However, no NMR spectroscopic data was supplied. Later, Simoyi and co-workers published X-ray crystallographic data on *N,N'*-dimethylthiourea dioxide, synthesised using a modified procedure reported by Repine.[49] Simoyi noted that the ratio of hydrogen peroxide:thiourea was strictly controlled at 2:1 in order to prevent formation of mixtures of oxyacids. They employed hydrogen peroxide, near acetone-dry ice temperatures of -59 ºC, without molybdate catalysts to afford the target dioxide on average 80% yield.

Simoyi and co-workers published a series of papers concerning the oxidation of thiourea using other oxidising agents. The oxidation of thiourea with bromate BrO_3^- was studied.[70] The work was mainly concerned with the kinetics and mechanism of the oxidation of thiourea. Isolation of postulated monoxide, dioxide and trioxide intermediates was not carried out. A paper in 1987 outlined the stepwise oxidation of thiourea, to the corresponding monoxide, dioxide and trioxide, with aqueous bromine.[71]

Finally in 2003, Denk and co-workers reported the isolation of a *N,N*-di-*tert*-butylimidazolin-2-ylidene sulfur dioxide adduct, which was also viewed as *N,N'*-di-*tert*-butylethylenethiourea-*S,S*-dioxide **9** (Scheme 14, 1.4.2.1). They reported the isolation of the dioxide from the reaction of the carbene and sulfur dioxide gas.[47]

1.4.2.4 Application of thiourea dioxides

Thiourea dioxide is utilised in the textiles industry for the bleaching process of wools.[72, 73] The wool is bleached with alkaline hydrogen peroxide, to remove stains, followed by treatment with thiourea. The unspent peroxides oxidise thiourea to thiourea dioxide. The dioxide is then hydrolysed to the urea and the sulfinate dianion, and subsequently functions as the reductive-bleaching agent. The whole process is known as full bleaching.



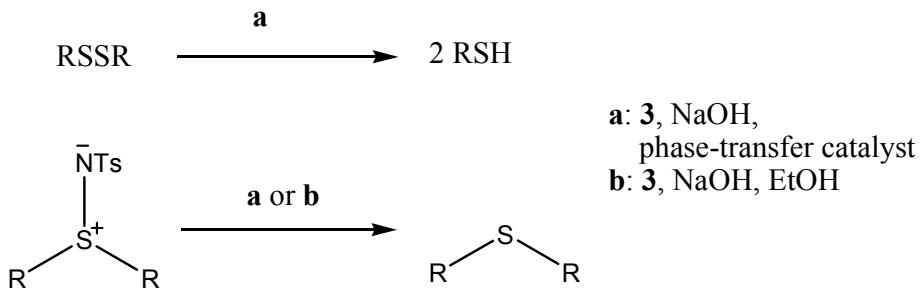
Scheme 18. Full bleaching of wool with alkaline hydrogen peroxide and thiourea

Thiourea dioxide was also studied as a source of molecular oxygen. Burgess and co-workers refluxed thiourea dioxide in anhydrous acetonitrile and detected thiourea, urea and dioxygen.[74]

However, thiourea dioxide is probably best known as a reducing agent. It has been used for the reduction of metal ions to their corresponding metals, including Cd(II),[75] Cu(II),[76] and Ni(II),[77] for the reduction of Fe(III) to Fe(II),[39] and ketones[78-81] and aldehydes[82] to the respective alcohols. The role of thiourea dioxide as a reducing agent for ketones was questioned by some authors. For example, it was discovered that thiourea dioxide was not required for the reduction of steroidal ketones in alcoholic potassium hydroxide. Consequently, it was suggested that the reduction took place *via* a Meerwein-Ponndorf type mechanism.[79]

A series of organosulfur substrates were successfully reduced with thiourea dioxide **3**. *N*-Tosylsulfimides and disulfides were also reduced to sulfides and thiols, respectively,

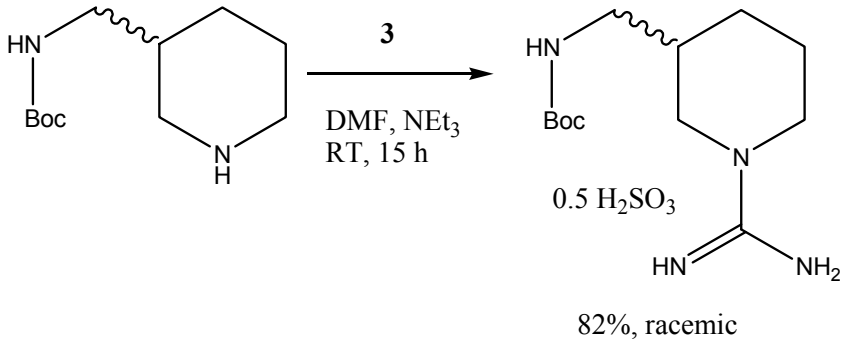
under heterogeneous and homogeneous conditions (Scheme 19).[83] Sulfoxides have also been reduced to the corresponding sulfide in high yields (> 89%) with thiourea dioxide and catalytic quantities of iodine.[84]



Scheme 19. Reduction[83] of disulfides and sulfimides with thiourea dioxide 3

The reduction of organotelluro- and organoseleno-compounds,[85] nitro[86, 87] and azo[87, 88] compounds has also been reported. Monomeric and polymeric organosilicon thiourea dioxides have been studied and were found to reduce Mn(VII) to Mn(IV).[81]

Thiourea dioxide **3** has been used in guanylation reactions. For example, guanylation was carried out by Hilpert and co-workers towards the synthesis of a racemic piperidinyl amidine as a building block for thrombin inhibitors.[89]



Scheme 20. Synthesis of guanidines[89] with thiourea dioxide

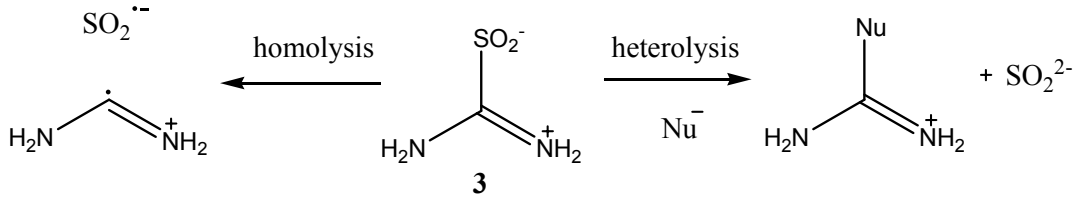
According to Makarov and co-workers, guanidines are formed from the nucleophilic attack of amines with thiourea dioxide.[90] Bischoff found that guanylation reactions were

more difficult with thiourea dioxides than with thiourea trioxides.[1] It was thought that thiourea dioxide decomposed too quickly in aqueous potassium carbonate before nucleophilic substitution with glycine could take place.[33]

1.4.2.5 Decomposition of thiourea dioxides

The mechanism of decomposition of thiourea dioxides is pH dependent.[34, 35, 53, 91] At neutral and low pH, thiourea dioxides tend to decompose to the formamidine or formamidinium salt, discussed in more detail in 1.4.3.2. At high pH, thiourea dioxides usually decompose to furnish a powerful, sulfur-containing reducing species.

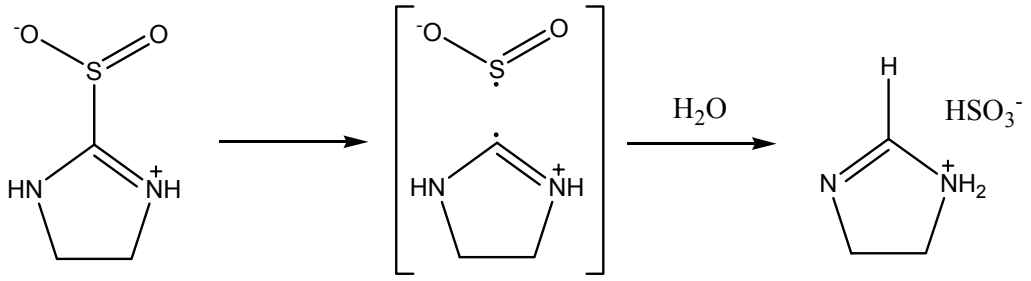
In general, reduction reactions with thiourea dioxide require the presence of strong base, usually sodium hydroxide.[35] The mechanism of reduction is still a matter of debate amongst the many authors who have supplied independent and sometimes conflicting results. The key question which has fuelled the debate was the mechanism of C-S bond dissociation *via* homolysis or heterolysis. Both mechanisms account for the formation of sulfur containing anions.



3

Scheme 21. Homolysis and heterolysis of the C-S bond in thiourea dioxide 3

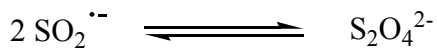
It was argued by McGill and Lindstrom that homolysis is likely to take place. The authors investigated the reduction of Cd(II) with thiourea dioxide and suggested that the reduction is effected by a carbon containing residue, as shown by the detection of carbon in the cadmium metal product.[75] To our knowledge, McGill and Lindstrom's report is the only example in which a sulfur containing anion (Scheme 21) is not the reducing species. According to Marshall, ethylenethiourea dioxide **6** dissociates homolytically at the C-S bond to give a radical ion pair, trapped in water (Scheme 22).[65]



6

Scheme 22. Homolytic dissociation of ethylenethiourea dioxide 6 in water[65]

The formation of the $SO_2^{\cdot-}$ radical anion is supported by EPR spectroscopic studies.[75, 78] What is agreed amongst the authors in this area is that thiourea dioxide acts as a precursor to a radical anion $SO_2^{\cdot-}$ and subsequently, dithionite $S_2O_4^{2-}$.[34, 35, 65, 75, 78, 92] Dithionite is formed *via* the dimerisation[93, 94] of the radical anion, as demonstrated by Creutz and Sutin, who also propose that the radical anion not dithionite, is the kinetic reducing species.[95]



Scheme 23. Formation of dithionite *via* dimerisation

The radical anion or dithionite was thought to be detected chemically with ammoniacal solutions[96] of naphthol yellow S or aqueous methylene blue solutions.[97] Sodium dithionite is commercially available and exhibits an EPR signal (singlet line[98, 99] at g = 2.0055) which is identical to the decomposition products of basic solutions of thiourea dioxide. As a result, thiourea dioxide has been compared numerous times with other $SO_2^{\cdot-}$ radical anion precursors, including sodium dithionite, sodium hydroxymethanesulfinate dihydrate $NaO_2SCH_2OH.2H_2O$ (Rongalite©) and zinc hydroxymethanesulfinate $Zn(O_2SCH_2OH)_2$ (Decroline©).[35, 78, 92, 100-103]

In particular, thiourea dioxide was compared as a reducing agent for ketones[78] and nitrites.[104] The formation of the $SO_2^{\cdot-}$ radical anion has been used to explain the

formation of pinacol products from the reduction of ketones[78] and initiation reactions regarding polymer synthesis.[105]

An alternative mechanism of heterolysis has been proposed by several authors. Budanov suggested that heterolytic cleavage is most likely to occur in protic solvents whereas homolytic cleavage is favoured in aprotic solvents and in the solid-state.[92] Simoyi and others proposed that anaerobic solutions of alkaline thiourea dioxide do not yield dithionite ions.[35] In other words, the radical anion is not thought to be the primary decomposition species but a secondary species. The formation of the $SO_2^{\cdot-}$ radical anion, and consequently dithionite, are dependent on the oxygen. For example, *N,N'*-dimethylthiourea dioxide is thought to yield the dianion SO_2^{2-} through nucleophilic substitution with hydroxide (compare with Scheme 21, Nu = OH).[49] The sulfinate dianion SO_2^{2-} was then thought to rapidly oxidise with dissolved molecular oxygen to afford the radical anion $SO_2^{\cdot-}$.[35] The reaction of ammonia and amines with thiourea dioxide is also thought to take place *via* nucleophilic substitution.[90]

The decomposition of thiourea dioxide was found to be comparable with that of sodium hydroxymethanesulfinate. The sodium salt is also thought to yield the radical anion, under aerobic conditions only.[92]

1.4.3 Thiourea trioxide

Thiourea trioxides, S = +4, comprise of the final oxidation state of thiourea in which the C-S bond remains intact. The lack of non-bonded electron pairs on sulfur in thiourea-*S,S,S*-trioxides means that further oxidation leads to C-S bond dissociation, forming the corresponding urea and sulfate, S = +6, species.[70, 106-108]

1.4.3.1 X-ray and computational studies of thiourea trioxides

The X-ray crystal structure of thiourea trioxide **4** has recently been elucidated by Simoyi and co-workers.[109] Thiourea trioxide is not commercially available and requires oxidation from either thiourea[110] or thiourea dioxide.[111, 112]

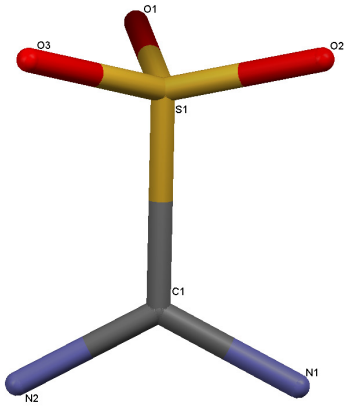


Figure 6. X-ray crystal structure of thiourea trioxide 4 (hydrogen atoms not supplied)[109]

The terminal sulfonate $-SO_3^-$ group lies adjacent to a planar amidine group. The C-S bond is 1.815 Å and is shorter than thiourea dioxide[45] at 1.8592 Å but still longer than thiourea[10] at 1.716 Å. The C-N bonds are 1.298 Å and 1.297 Å, and are shorter than the C-N single bond covalent radii of 1.51 Å.[11] The N-Ĉ-N bond angle is 124.1 º. The short C-N bonds and planar amidine geometry are thought to be due to the donation of the nitrogen lone pair of electrons towards carbon. The S-O bonds are between 1.431-1.446 Å and shorter than those in thiourea dioxide of 1.4997 Å. The three O-Ŝ-O bond angles of the tetrahedral sulfonate group are between 112.76-115.59 º.[109]

The density was calculated to be 1.948 g cm^{-3}.[8] ^{13}C NMR spectroscopic data for the amidine carbon is 166.13 ppm in deuterium oxide.[109] The X-ray crystallographic data are listed in Table 3 for comparison with other derivatives of thiourea trioxide.

Svarovsky carried out semi-empirical AM1 and *ab initio* HF calculations to show that thiourea trioxide was zwitterionic in the solid state, gas phase and in solution,[8] unlike thiourea dioxide which is thought to tautomerise to the neutral form on dissolution.[40]

In 1971, Walter and Holst published X-ray crystallographic data of *N,N*-dimethylthiourea trioxide **14**.[113]

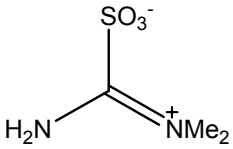
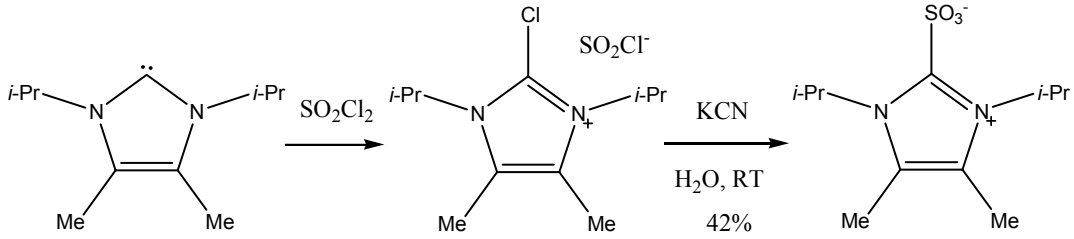


Figure 7. *N,N*-Dimethylthiourea trioxide 14

The trioxide **14** was synthesised from the peracetic acid oxidation of the respective thiourea.[113] The trioxide **14** possesses a tetrahedral sulfonate group with a planar amidine moiety. The Me_2N-C bond length is 1.304 Å and shorter than the H_2N-C bond, at 1.312 Å. Other X-ray structural data supplied by Walter and Holst are listed in Table 3.

Kuhn and co-workers obtained an X-ray crystal structure of *N,N'*-diisopropyl-4,5-dimethylimidazolium-2-sulfonate **16**.[114] This was prepared from the hydrolysis of a chlorosulfite salt **15** in the presence of potassium cyanide (Scheme 24).



15 **16**

Scheme 24. Synthesis[114] of *N,N'*-diisopropyl-4,5-dimethylimidazolium-2-sulfonate 16

The structure of the thiourea trioxide derivative **16** was similar to thiourea trioxide **4** and *N,N*-dimethylthiourea trioxide **14**. The X-ray crystallographic data are listed in Table 3.

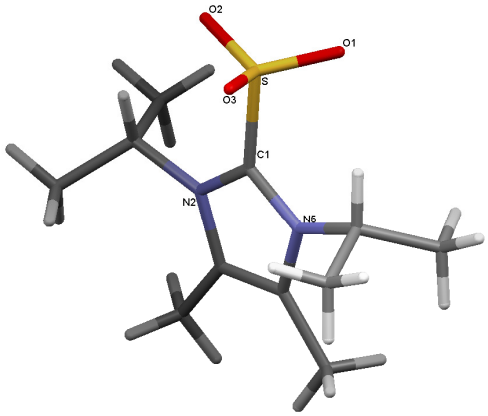
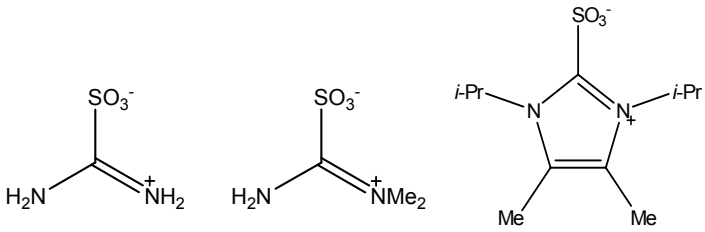


Figure 8. X-ray crystal structure[114] of *N,N'*-diisopropyl-4,5-dimethylimidazolium-2-sulfonate 16



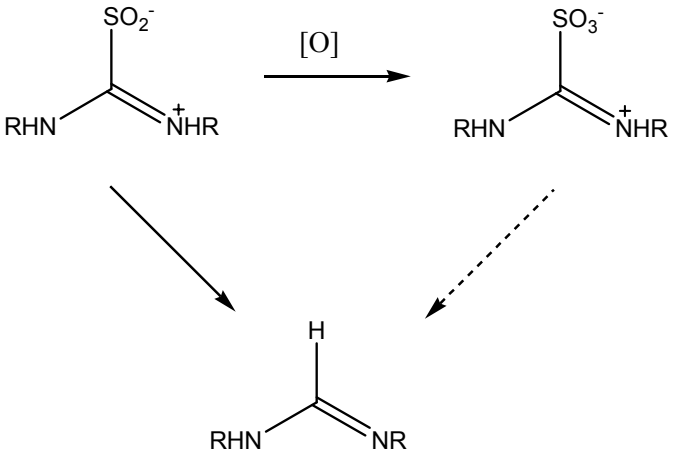
	4	**14**	**16**
C-S /Å	1.815	1.827	1.822
S-O /Å	1.431-1.446	1.439-1.448	1.4310-1.4413
amidine C-N /Å	1.298/1.297	1.312/1.304	1.347/1.347
N-Ĉ-N /º	124.1	123.5	108.53
O-Ŝ-O /º	112.76-115.59	113.5-115.3	113.11-115.95
CS ^{13}C NMR /ppm	166.13 (D_2O)	Not given	145.88 ($CDCl_3$)
Lit. Reference	111	115	116

Table 3. Literature thiourea trioxide derivatives

1.4.3.2 Synthesis of thiourea trioxides

The synthesis of thiourea trioxide is usually carried out with peracetic acid.[110] In general, the stability of trioxides is thought to be higher than the corresponding dioxides.[1, 65] Thiourea trioxide formation is often accompanied by formamidine formation. Some groups found that decomposition of thiourea trioxides is not responsible for formamidine

formation but is due to dioxide decomposition.[66, 115, 116] The decomposition pathway is summarised in Scheme 25.



Scheme 25. Decomposition of thiourea-dioxide and -trioxide derivatives

In 1969, Walter and Randau published two papers which described the synthesis of a range of mono- and di-substituted thiourea trioxides.[110] They oxidised a series of *N*-alkyl and *N*-aryl substituted thioureas with peracetic acid, in methanol below -5 ºC, to afford the corresponding trioxides at 29-90% yields. Additionally, they oxidised thiourea monoxides and dioxides with peracetic acid, in methanol below -10 ºC, to give the trioxide. In some cases, for example oxidation of *N,N'*-di-*tert*-butylthiourea monoxide with peracetic acid, only trioxide-methanol adducts were isolated as determined from elemental analysis.[110] In another publication, they isolated a series of *N,N*-dialkyl-*N'*-(2,6-dialkylphenyl)thiourea trioxides (Figure 9) from the oxidation of the thiourea precursor with peracetic acid in chloroform at -20 ºC.[117] Yields ranged from 56-80%.

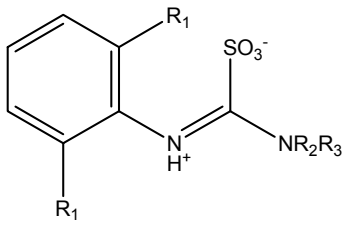
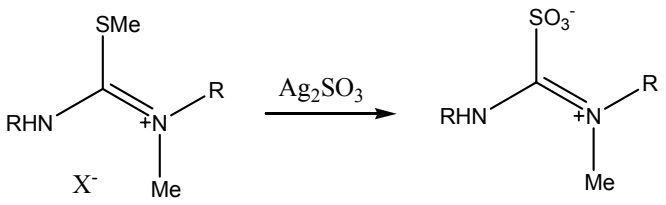


Figure 9. *N,N,N'*-Trisubstituted thiourea trioxides[110]

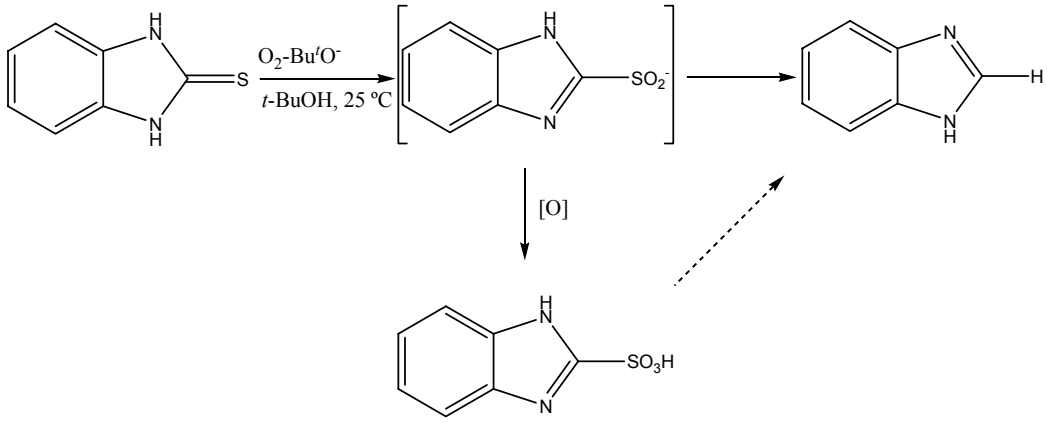
Both papers reflected on the sulfonate stretching modes, thought to reside in the 1290-1220 cm^{-1} (asymmetric) and 1065-1048 cm^{-1} (symmetric) regions.[110, 117]

Walter and Rohloff prepared a range of substituted thiourea trioxides from the reaction of *S,N,N,N'*-tetrasubstituted thioureas with silver sulfonate.[118]



Scheme 26. *S,S,S*-Trioxides from *S*-methyl thioureas[118]

Kim and co-workers found that the oxidation of benz- and naphtha-imidazole-2-thiols with oxygen and *tert*-butoxide, gave mixtures of the corresponding imidazoles and *S,S,S*-trioxides.[115] The product distribution was thought to be solvent dependent. They proposed that benzimidazole was formed from the decomposition of the dioxide formed *in situ* and not from the decomposition of the trioxide.



Scheme 27. Alkaline oxidation[115] of benzimidazol-2-thiol

Marshall and Singh reported the synthesis of ethylenethiourea trioxide from hydrogen peroxide oxidation of an ice-cold suspension of ethylenethiourea in carbon tetrachloride. *N,N'*-Dimethylethylenethiourea trioxide was subsequently prepared from the reaction of the ethylenethiourea trioxide with an excess of diazomethane at room temperature. No yields were given.[28]

Bischoff prepared a series of mono- and di-arylthiourea trioxides from the oxidation of the thiourea with peracetic acid in either methanol or dichloromethane.[1] From the study, it was found that the isolation of the trioxide was sensitive to protic solvents and was thought to be due to the low stability of preceding dioxide. Bischoff also discovered that oxidation was temperature sensitive. An optimum temperature was required, for example, for the formation of thiourea trioxide > 10 ºC, in order to prevent precipitation of thiourea dioxide intermediates and to speed up the apparent slow oxidation of the dioxide.

In 1995, Casida and co-workers revisited the oxidation of ethylenethiourea.[66] They claimed to have deduced the ^{1}H NMR spectroscopic data of the monoxide, dioxide and trioxide of ethylenethiourea in deuterium oxide. The authors isolated ethylenethiourea trioxide from two published procedures, using hydrogen peroxide and anion exchange purification to afford the target trioxide. They also identified decomposition products,

including imidazolidin-2-one and 2-imidazoline. The authors deduced that formation of 2-imidazoline was due to the decomposition of ethylenethiourea dioxide and not from the decomposition of ethylenethiourea trioxide.

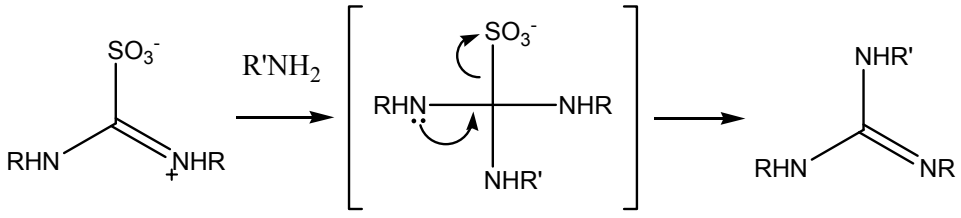
Pan published a procedure for the synthesis of thiourea trioxide from thiourea dioxide with hydrogen peroxide.[111] They employed acidic conditions at 50 ºC in order to achieve 93% yield of thiourea trioxide from thiourea dioxide.

As mentioned above, Kuhn had synthesised *N,N'*-diisopropyl-4,5-dimethylimidazolium-2-sulfonate **16** using a procedure which did not involve the oxidation of either thiourea or thiourea dioxide precursors.[114]

1.4.3.3 Reactivity and application of thiourea trioxides

Thiourea trioxide derivatives have been utilised as guanidylating reagents (Scheme 9, 1.3). The reaction has been carried out with primary amines[119] and anilines.[120, 121]

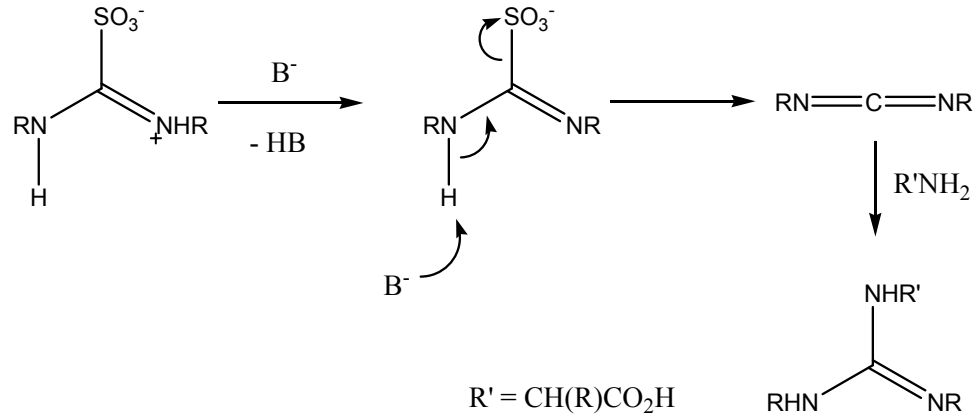
The reactivity of thiourea trioxide is considered lower than thiourea dioxide[1, 110] and is thought to be attributed to the shorter C-S bond in the trioxide *cf.* the dioxide.[122] In her thesis, Bischoff considered two pathways for guanylation of amino acids: nucleophilic substitution and elimination.[1] Nucleophilic substitution was thought to take place through the formation of a tetrahedral intermediate followed by expulsion of a sulfur-containing moiety.



R' = $CH(R)CO_2H$

Scheme 28. Substitution mechanism for formation of guanidines[1]

Alternatively, elimination with base (B, Scheme 29) to give the corresponding carbodiimide, was proposed. The carbodiimide would then be susceptible to nucleophilic attack.



Scheme 29. Elimination mechanism for formation of guanidines[1]

Bischoff found that guanylation reaction yields were improved at high pH. Attempts to prepare the guanidines from authentic carbodiimides and glycine failed. Bischoff concluded that guanylation of glycine probably proceeded through a nucleophilic substitution mechanism (Scheme 28).

Hydrolysis of thiourea trioxide at neutral pH gave predominantly urea, through nucleophilic substitution. At higher pH, elimination was favoured as demonstrated by the detection of carbodiimide HN=C=NH and cyanamide NH_2CN.[1, 33]

1.5 Objectives

Thiourea dioxide is a versatile reducing agent although its synthetic utility is still confined and largely unexplored. Much of the apparent low stability of the derivatives of thiourea dioxide remains untapped.

The objectives of research are as follows:

- Synthesis of novel derivatives of thiourea-*S,S*-dioxide **3**

- Reduction of a series of new, as well as established substrates with thiourea dioxide derivatives
- Investigation into the mechanism of decomposition of thiourea dioxides *via* the reduction of sulfimides and SET probes
- Development of the potential for thiourea dioxides as diaminocarbene precursors

Chapter 2. Synthetic and computational studies of *N,N'*-disubstituted thiourea dioxide derivatives

2.1 Establishing and developing published procedures

As described in chapter 1, it was not possible, on the basis of the existing literature, to be confident about the reproducibility of published syntheses. In light of conflicting literature reports, we decided to commence with our own investigations of synthetic routes to thiourea dioxides.

In particular, De Filippo and co-workers published their findings on the synthesis of *N,N'*-diphenylthiourea dioxide.[58] However, Bischoff's attempts to isolate *N,N'*-diphenylthiourea dioxide, including the use of procedures reported by De Filippo, were unsuccessful.[1] Bischoff found that some of the literature on the synthesis of dioxides and trioxides of thiourea was in error. Thus, it was of high priority that the validity of a selection of literature procedures be established; those chosen are outlined below.

Walter and Randau have published work on the synthesis of thiourea dioxide derivatives.[53] Interestingly, they isolated *N,N'*-dicyclohexylthiourea dioxide and *N,N'*-di-*sec*-butylthiourea dioxide but not *N,N'*-di-*tert*-butylthiourea dioxide. The correlation found between structure and isolation provided an opportunity for further study for our work.

The degradation of the *S*-oxides of ethylenethiourea was investigated by Marshall[28] and Casida.[66] Both papers agreed on the apparent low stability of ethylenethiourea dioxide and isolation was unsuccessful. Work published on the synthesis of derivatives of ethylenethiourea dioxide *via* the oxidation of the thiourea precursor remains unreported to date and was one area of research which was of interest.

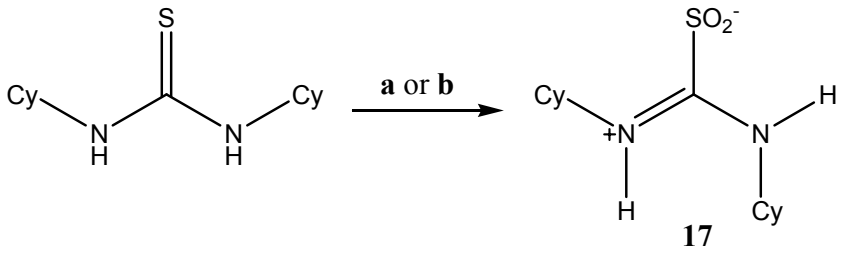
Crank and Mursyidi investigated the dye-sensitised oxidation of a range of thioureas.[69] Unfortunately, only thiourea dioxide from thiourea could be isolated. The majority of the

remaining substituted alkyl and aryl thioureas gave mixtures of products with concomitant evolution of sulfur dioxide gas. The use of singlet oxygen was deemed inappropriate for our purposes and was not investigated further.

Work in this project therefore began by investigating the validity and scope of published work: the synthesis of *N,N'*-dicyclohexylthiourea dioxide **17**, *N,N'*-di-*tert*-butylthiourea dioxide **18**, *N,N'*-diphenylthiourea dioxide **19** and the derivatives of ethylenethiourea dioxide, all of which is described in 2.1.1–2.1.3. It was eventually discovered that isolation of **17** was easier than the other dioxide derivatives **18** and **19**.

2.1.1 Oxidation of *N,N'*-dialkylthiourea derivatives

N,N'-Dicyclohexylthiourea dioxide **17** was successfully isolated following a procedure described by Walter,[53] referred to as non-catalytic oxidation in this thesis, and by Bischoff, referred to as catalytic oxidation.[1]



17

a: Walter conditions: 13 equiv. H_2O_2, MeOH, RT
b: Bischoff conditions: 2 equiv. H_2O_2,
$Na_2MoO_4.2H_2O$, 1,4-dioxane, Et_2O, 2 °C

Scheme 30. Oxidation[53] of *N,N'*-dicyclohexylthiourea

The resultant dioxide **17** was found to be highly insoluble and difficult to characterise fully. The dioxide **17** was insoluble in standard hydrocarbon, alcohol or chlorinated based solvents, water, DMF or dimethylsulfoxide. It dissolved in d_6-dimethylsulfoxide when heated to 50 ºC, but gave complex spectra on NMR spectroscopic analysis.

Ammoniacal solutions of naphthol yellow S are specific tests for dithionite $S_2O_4^{2-}$ ions.[96] Dithionite ions are generally accepted as the species formed from the decomposition of

thiourea dioxides at high pH and are discussed in more detail in chapter 4.[35] *N,N'*-Dicyclohexylthiourea dioxide was insoluble in this test solution and returned a negative result for dithionite ions.

The IR spectra of thiourea dioxides are characterised by a sharp absorption in the 1200-1000 cm^{-1} region, corresponding to the asymmetric ν_{as} and symmetric ν_s stretching modes of the terminal sulfinate $-SO_2^-$ group.[53] Walter also proposed the sulfonate $-SO_3^-$ IR stretching modes[110] that neighbour the sulfinate region, as listed in Table 4.

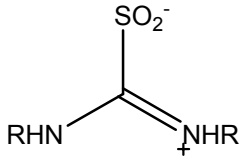
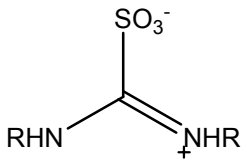
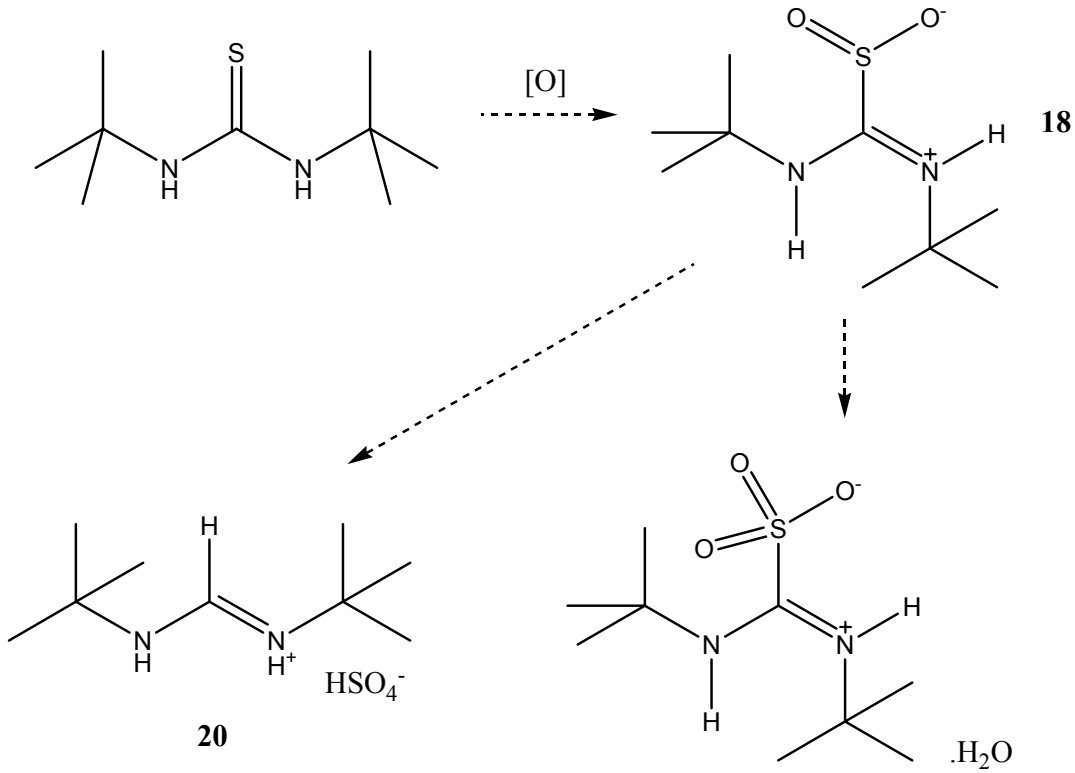
	ν_{as}(SO) /cm^{-1}	ν_s(SO) /cm^{-1}
	1099-1080	1020-1005
	1290-1220	1065-1048

Table 4. IR asymmetric and symmetric stretching modes of *N,N'*-disubstituted thiourea-dioxides[53] and trioxides[110]

The IR, melting point and elemental analysis of *N,N'*-dicyclohexylthiourea dioxide synthesised in this work were in agreement with Walter's work. The compound was found to be air stable under ambient conditions as determined by IR spectroscopy.

N,N'-Di-*tert*-butylthiourea dioxide **18** could not be isolated using Walter's conditions nor using Bischoff's conditions. The product tested negative for dithionite ions suggesting that the dioxide was unlikely to be present. Elemental and IR analysis of the product revealed the formation of either the sulfonic acid monohydrate or formamidinium bisulfate salt **20** (Scheme 31; elemental analysis gave C, 42.88; H, 8.74; N, 10.32; salt **20** requires C, 42.50; H, 8.72; N, 11.01%). The formamidinium salt was detected from NMR spectroscopic data, in particular by the non-exchangeable deshielded

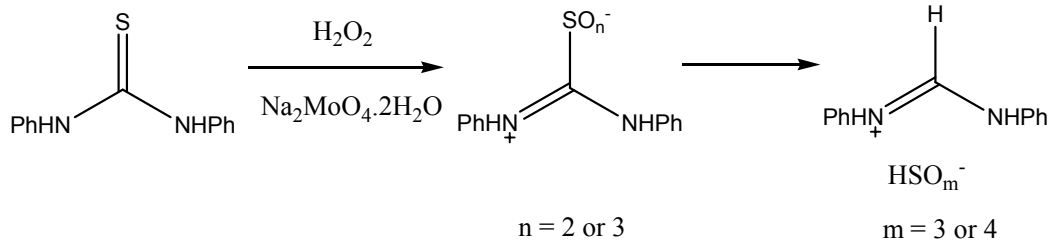
formamidinium CH peak at 7.86 ppm (coupled to ^{13}C at 151.8 ppm from HMQC NMR experiments).



Scheme 31. Decomposition of *N,N*'-di-*tert*-butylthiourea dioxide 18

2.1.2 Oxidation of *N,N'*-diphenylthiourea

Attempts to isolate *N,N'*-diphenylthiourea dioxide **19** *via* De Filippo's (catalytic) procedure[58] were unsuccessful. IR spectroscopic analysis revealed an apparent mixture of the corresponding dioxide and trioxide of *N,N'*-diphenylthiourea **8**. Elemental analysis was inconclusive; however, sulfur was detected. Analytical techniques which involve the dissolution of the unknown mixture gave a strong indication of a formamidine or formamidinium salt. For example, a non-exchangeable CH signal was identified by HMQC NMR spectroscopy (^1H 9.17 ppm coupled to ^{13}C 151.7 ppm, in d_6-dimethylsulfoxide) and a formamidinium cation was characterised by mass spectrometry. The anion was thought to be either a bisulfite or bisulfate counter anion (Scheme 32).



Scheme 32. Synthesis and decomposition of *N,N'*-diphenylthiourea dioxide 19 (n = 2)

From our work, oxidation at the sulfur centre was thought to weaken the C-S bond and lead to facile elimination of a sulfur containing anion. This result differs from the work by Smith and Williams, who propose that *N,N'*-diphenylthiourea is oxidised at the *para*-position of the aniline group *in vivo*.[30] The mechanism of elimination is discussed in more detail in chapters 4 and 5.

Literature procedures describe purification *via* recrystallisation from water or methanol[58] or by washing the crude mixture with water.[59] In our work, the product mixture was found to be water and methanol soluble which was not in agreement with literature procedures. The unknown product tested negative for dithionite ions. Therefore, the dioxide is probably not in the mixture or of too low concentration thus preventing a positive test.

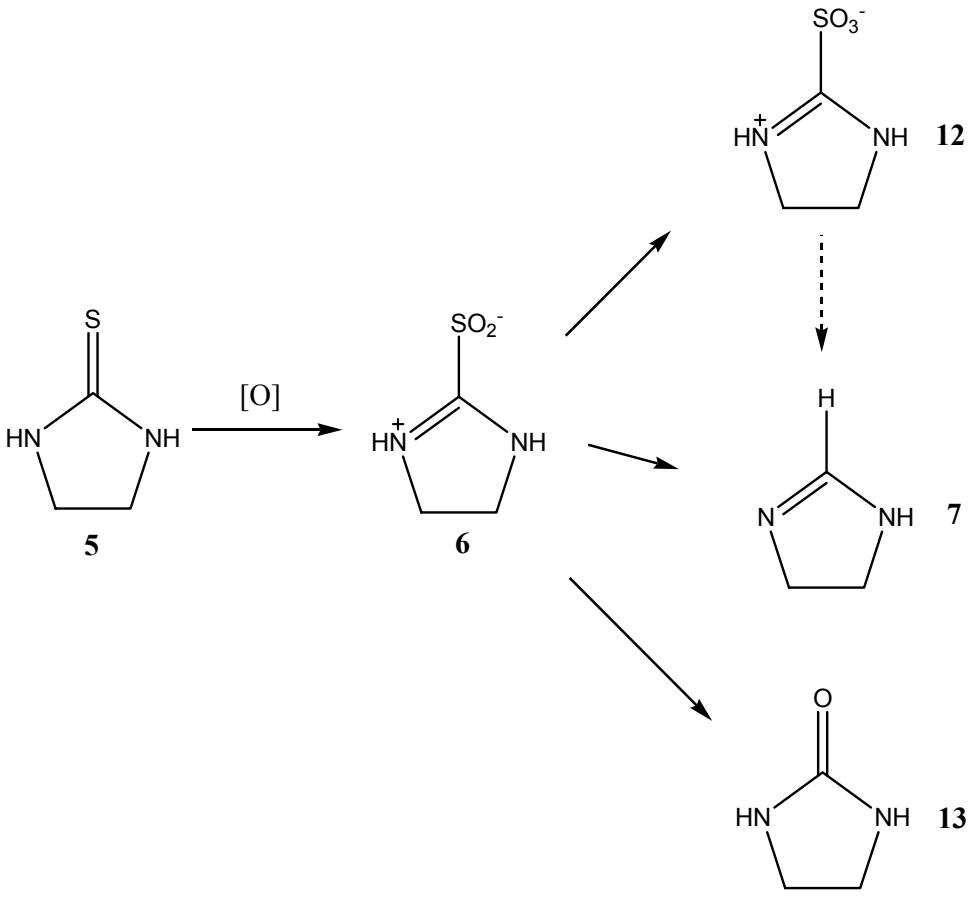
It appears that *N,N'*-diphenylthiourea dioxide is too unstable to isolate. Moreover, observations in solution were thought to correspond to a compound where cleavage of the C-S bond had taken place. Whether C-S bond dissociation occurs after dissolution remains unknown. Overall, the difficulties in isolating *N,N'*-diphenylthiourea dioxide encountered from our studies are similar to findings reported by Bischoff.[1]

2.1.3 Oxidation of ethylenethiourea derivatives

A study of the oxidation of ethylenethiourea **5** was reported in the literature by Marshall,[28] and Casida and co-workers.[66] Unfortunately, they could not successfully isolate the corresponding dioxide **6,** using hydrogen peroxide. Both authors investigated

the decomposition of ethylenethiourea dioxide using NMR spectroscopy. We also found that ethylenethiourea dioxide was too difficult to isolate. The reaction was carried out several times, using two equivalents of hydrogen peroxide, under catalytic and non-catalytic conditions (Scheme 30, 2.1.1).

The best results were obtained with catalytic conditions[1] and with non-catalytic conditions[28] using carbon tetrachloride as a solvent. Both reactions gave suspensions (Scheme 33) and were filtered in order to isolate the dioxide. The crude samples tested positive for dithionite ions and demonstrated apparent SO_2 and SO_3 stretching modes in the IR spectrum. Our findings from NMR spectroscopic analysis corresponded to the data reported by Casida,[66] that is a mixture of imidazolidin-2-one **13**, 2-imidazoline **7**, ethylenethiourea-dioxide **6** and -trioxide **12**.

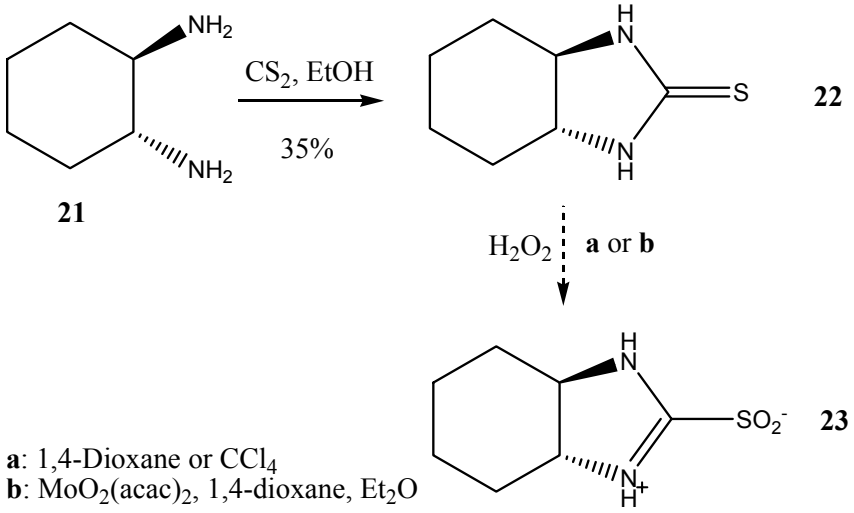


Scheme 33. Synthesis and decomposition[66] of ethylenethiourea dioxide

It was apparent that the oxides of ethylenethiourea were very unstable in solution from NMR experiments (in deuterium oxide) and could not be isolated. The NMR sample, obtained from the catalytic oxidation of ethylenethiourea, was analysed after standing at room temperature for 24 hours and found to contain a higher concentration of 2-imidazoline **7** and unchanged concentration of imidazolidin-2-one **13** but no sign of the respective dioxide **6**. Similar observations in the NMR spectrum were made when non-catalytic conditions (using carbon tetrachloride as a solvent) were employed. When using ethanol as a solvent under non-catalytic conditions, the dioxide was not detected at all in either fresh or 24 hour-old samples. This suggests that the dioxide of ethylenethiourea may have decomposed to 2-imidazoline. The decomposition of the dioxide **6** is in agreement with the synthetic investigations by Casida. The formation of 2-imidazoline is also observed *in vivo* by Deorge and Takazawa, who propose that ethylenethiourea is oxidised by thyroid peroxidase and rapidly decomposes to 2-imidazoline.[29]

No further work was carried out towards the isolation of ethylenethiourea dioxide. In light of the apparent instability of the dioxide in solution, especially aqueous media, it was thought more hydrophobic analogues of ethylenethiourea dioxide would prove easier to isolate.

A bicyclic analogue, *trans*-4,5-tetramethyleneimidazolidine-2-sulfinic acid **23**, was chosen as the next target. The precursor, *trans*-4,5-tetramethyleneimidazolidin-2-thione **22**, was synthesised from the diamine **21** and carbon disulfide as outlined in Scheme 34.[123] The oxidation of the thiourea was carried out analogously to literature procedures under non-catalytic[53, 66] and catalytic[1, 58] conditions.

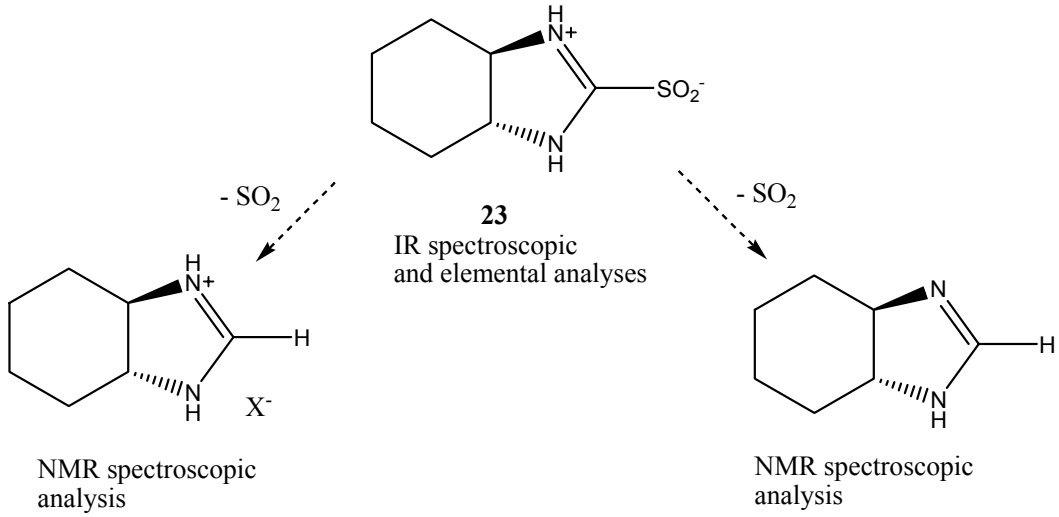


Scheme 34. Synthesis of *trans*-4,5-tetramethyleneimidazolidine-2-sulfinic acid 23

A reaction of the thiourea with hydrogen peroxide in 1,4-dioxane was carried out and monitored by near-IR spectroscopy. 1,4-Dioxane is miscible with aqueous hydrogen peroxide and gave a relatively blank near-IR spectrum. 1,4-Dioxane was therefore used in preference to other water miscible solvents such as acetonitrile, ethanol or THF. Aliquots were taken from the homogeneous mixture after 10 minutes and 20 minutes and found to test positive for dithionite ions. After 30 minutes no dithionite ions were detected. NMR and IR spectroscopic analyses of the crude product mixture revealed what was most likely to be the corresponding urea, *trans*-4,5-tetramethyleneimidazolidin-2-one **24**. Near-IR spectroscopic monitoring appear to show two processes occurring (see appendix) as shown by the appearance of two peaks at *ca.* 5322 cm^{-1} (time = 0 minutes) and *ca.* 7000 cm^{-1} (time = 4 minutes). Unfortunately, no further conclusions could be made. The reaction was monitored for a further 45 minutes, and resulted in no significant change to the spectrum.

The oxidation of *trans*-4,5-tetramethyleneimidazolidin-2-thione **22** was repeated using non-catalytic conditions, with carbon tetrachloride as the solvent. After 40 minutes, a white suspension that formed was filtered. The white solid tested positive for dithionite ions and the sulfinate group could be characterised from the IR spectrum. The NMR

spectrum was complex and appeared to contain formamidinium salt or formamidine-type signals. The integration of the amidine CH peak at *ca.* 8.3 ppm was found to increase relative to the other cyclohexane methylene peaks when repeating the NMR spectroscopic analysis after 4 days. The theoretical composition for *trans*-4,5-tetramethyleneimidazolidine-2-sulfinic acid is C: 44.66, H: 6.43, N: 14.87 and S: 17.03%. The composition of the product from this work was C: 42.03, H: 6.14, N: 13.92 and S: 16.52%. The combined observations from elemental and NMR spectroscopic analyses gave rise to our proposal that the dioxide decomposes to a formamidine or formamidinium salt (Scheme 35) in the NMR solvent, d_6-dimethylsulfoxide.



Scheme 35. Decomposition of dioxide 23 on dissolution

The mechanism of decomposition of dioxide **23** is unknown but could take place *via* a carbene intermediate, analogous to the mechanism[116] proposed by Grivas and Ronne. This is discussed in more detail in chapters 4 and 5.

Oxidation of **22** under catalytic conditions resulted in a white suspension after 40 minutes. After filtration, the crude precipitate was found to contain the sulfinate as characterised by IR spectroscopy and also tested positive for dithionite ions. The NMR spectrum was too complex to interpret. The filtrate was found to contain a crude mixture

of the starting thiourea **22** and *trans*-4,5-tetramethyleneimidazolidin-2-one **24** as determined by NMR spectroscopy.

In summary, it appears that isolation of the ethylenethiourea dioxide derivatives investigated, prepared *via* the oxidation of the respective ethylenethiourea precursors, proved difficult. The non-catalytic oxidation of *trans*-4,5-tetramethyleneimidazolidin-2-thione with hydrogen peroxide in carbon tetrachloride proved to be the best result.

It was becoming clear that identification of disubstituted thiourea dioxide targets would need to be refined in view of the potential number of analogues available. The challenge was also compounded by the fact that most substituted thioureas of interest were not commercially available and that some careful consideration would need to be made before committing time to synthesising the thioureas. Computational studies of thiourea dioxide have been published by several authors and found to show good agreement with the X-ray crystal structure of thiourea dioxide. It was therefore decided that computational studies would be employed in order to investigate the structure of thiourea dioxide derivatives and subsequently identify isolable targets.

2.2 Computational studies of thiourea dioxide

Both X-ray crystallographic[38, 42-45] and computational[40, 42, 45, 47] work reported in the literature have reflected on the rather unusually long C-S bond in thiourea dioxide and extensive hydrogen bonding present within the crystal lattice. It was envisaged that the long C-S bond could be a major contributor to the stability of thiourea dioxides and therefore we decided to identify isolable thiourea dioxides based on their predicted C-S bond length.

The C-S bond length was determined from geometry optimisations. Subsequent vibrational frequencies were then calculated to establish the nature of the stationary point, *i.e.* that a local minimum was found. The IR spectrum of the thiourea dioxide derivative

could also be predicted from vibrational frequency calculations and was thought to prove useful in characterising the sulfinate group.

Density functional theory[124] DFT was chosen as the level of theory for the calculations. In particular, the B3LYP functional[125, 126] was employed given the repeated success at modelling organic molecules with sufficient calculation speed and level of detail. The zwitterionic form of thiourea dioxide is generally accepted as the best representation of thiourea dioxide in the solid state[38] and formed the structural basis of all calculations reported herein. All calculations were carried out using Gaussian03W with 6-31G(d,p) to 6-311+G(2df,p) basis sets.[127]

Initially, a series of B3LYP 'gas phase' geometry optimisations and vibrational frequency calculations were carried out on thiourea dioxide in order to investigate the effect of the polarisation and diffuse functions. In general, calculated C-S bond lengths were found to have improved agreement with X-ray crystallographic data with the inclusion of more d polarisation functions (entry 1 *cf.* 2) followed by the addition of + diffuse functions (entry 2 *cf.* 3). C-S bond lengths and SO_2 stretching frequencies were substantially improved when the geometries were optimised in solution (entries 4-5). The effect of the solvent model was thought to simulate the crystal packing of thiourea dioxide in the solid state. Solution phase calculations were carried out using an Integral equation formalism polarisable continuum model IEFPCM, provided in Gaussian03W, using solvents with high dielectric constants, such as water and acetonitrile. A selection of these data is listed in Table 5 and a full table of the basis set correlations are summarised in the appendix.

	Basis	$\nu_s(SO_2)$ /cm^{-1}	$\nu_{as}(SO_2)$ /cm^{-1}	S-O /Å		C-S /Å
1	[a]6-311G(d,p)	1038	1187	1.49982	1.48061	2.20783
2	[a]6-311G(3d,p)	1048	1198	1.48655	1.47037	2.08133
3	[a]6-311+G(3d,p)	1037	1173	1.48905	1.47551	2.04655
4	[b]6-311+G(d,p)	952	1002	1.52373	1.52083	1.93957
5	[b]6-311+G(3d,p)	993	1063	1.50124	1.49982	1.92449
6	X-ray[45]	[c]999	[c]1071	1.4997		1.8592

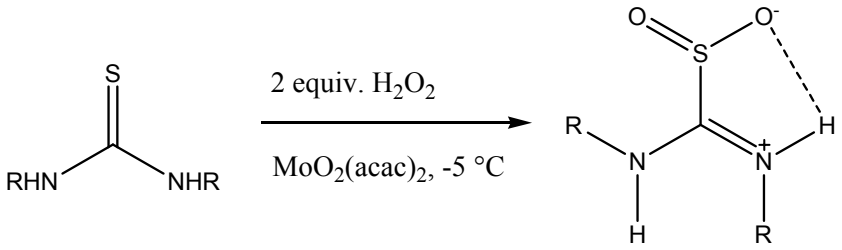
a: gas phase; **b**: IEFPCM (water); **c**: IR (KBr discs)

Table 5. Effect of basis set on the optimisation of thiourea dioxide

A full geometry optimisation and vibrational frequency calculation with B3LYP 6-311+G(3d,p) in water for thiourea dioxide **3** could be completed in approximately 4 days with current computing power. More expensive calculations *e.g.* B3LYP 6-311+G(2df,p) yielded no improvement in the geometry of **3**. Therefore, further development of the basis set was finalised: 6-311+G(3d,p) in water was chosen as the basis set for X-ray crystal predictors for the derivatives of thiourea dioxide.

2.3 Computational study and synthesis of novel thiourea dioxides

Two novel compounds, *N,N'*-diisopropylthiourea dioxide **25** and propylenethiourea dioxide **26** were modelled with DFT B3LYP 6-311+G(3d,p) in water, described previously, with the intention that the structures could be predicted computationally in reasonable time and synthesised with a few steps. The computational data revealed intramolecular hydrogen bonding between NH and O in the thiourea dioxides, as shown in Table 6.



Scheme 36. Catalytic oxidation of thiourea derivatives

R	$\nu_s(SO_2)$ /cm^{-1}	$\nu_{as}(SO_2)$ /cm^{-1}	C-S /Å	O-HN /Å
3, H	993	1063	1.92449	2.16973
25, *i*-Pr	994	1062	1.94696	2.02310
26, -$(CH_2)_3$-	995	1054	1.91320	2.21256
(X-ray) **25**, *i*-Pr	1009	1080	1.9045	2.127

Table 6. Calculated geometries and vibrational frequencies of *N,N'*-disubstituted thiourea dioxides from DFT B3LYP 6-311+G(3d,p) in water

As shown from the computational data listed in Table 6, it appears that the vibrational frequencies of propylenethiourea dioxide and *N,N'*-diisopropylthiourea dioxide at the sulfinate site are almost identical to the parent dioxide. The agreement of the sulfinate IR stretching modes between this work and that of Walter's work (Table 4, 2.1.1) was also encouraging.

The thioureas were oxidised under catalytic conditions with hydrogen peroxide. The isolation of *N,N'*-diisopropylthiourea dioxide is discussed in 2.3.1 and propylenethiourea dioxide in 2.3.2. Investigations into *N,N'*-diaryl derivatives follow in 2.4, with reference to computational data, that ultimately led to the isolation of a stable diaryl derivative.

2.3.1 Dioxide and trioxide of *N,N'*-diisopropylthiourea

It turned out that *N,N'*-diisopropylthiourea dioxide **25** was very simple to prepare in 80% yield and without the need for any purification. An X-ray crystal structure was obtained

and compared with the literature crystallographic data of thiourea dioxide (Table 2, 1.4.2.1).

The NMR sample was submitted using d_1-chloroform, d_6-dimethylsulfoxide and d_7-DMF, all of which showed the same set of peaks both by integration and by the number of environments. The ^{1}H NMR spectrum of the product at first sight appears as two compounds due to the two sets of methyl and methine proton signals. This was thought to arise due to intramolecular hydrogen bonding taking place leading to a structure with differing methyl and methine environments (Figure 10).

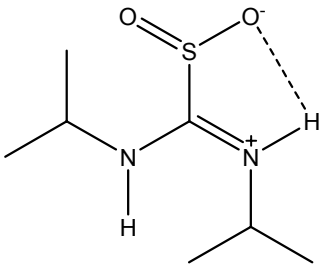


Figure 10: Intramolecular hydrogen bonding of *N,N'*-diisopropylthiourea dioxide 25 in solid and solution phases

The NMR observations for dioxide **25** are supported by the computational structure (Figure 11).

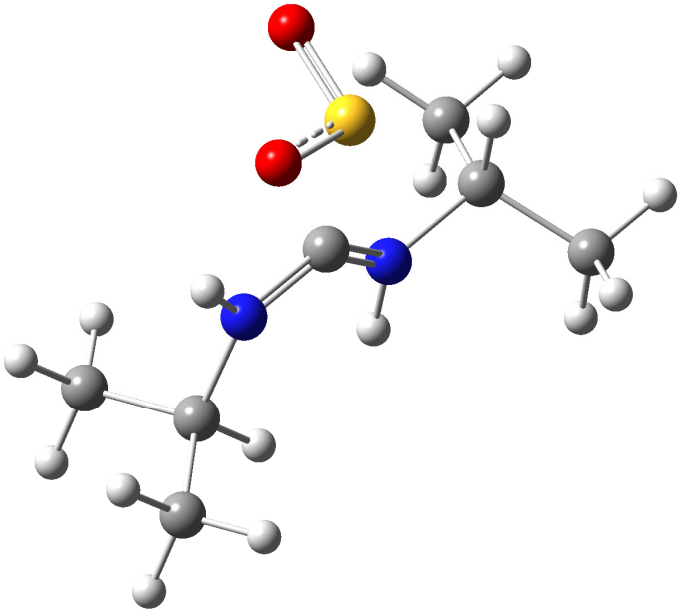


Figure 11. DFT predicted structure of *N,N'*-diisopropylthiourea dioxide 25

As determined from X-ray crystallographic studies, the C-S bond length at 1.9045 Å is longer in the isopropyl dioxide **25** compared with thiourea dioxide[45] 1.8592 Å. The bond length difference was also calculated to be longer (Table 6, 2.3).

The X-ray structure of the monomeric unit (Figure 12) was comparable to the DFT predicted structure. The X-ray crystal structure was characteristic of a planar amidine moiety which suggests double bond character *i.e.* donation of electrons towards the sulfinate group. Key X-ray crystallographic data of the thiourea dioxide moiety are listed in Table 7.

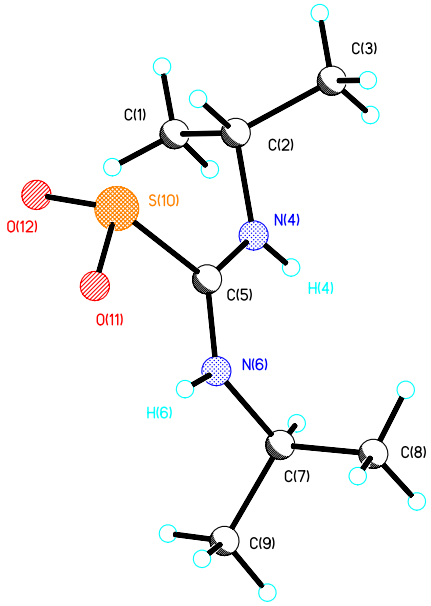


Figure 12. X-ray crystal structure of an asymmetric monomer of *N,N'*-diisopropylthiourea dioxide 25

Bond length /Å		Bond and dihedral angle /º	
C(5)-S(10)	1.9045(14)	O(11)-S(10)-O(12)	112.50(7)
C(2)-N(4)	1.4786(19)	O(11)-S(10)-C(5)	98.66(6)
N(4)-C(5)	1.3082(18)	O(12)-S(10)-C(5)	99.63(6)
C(5)-N(6)	1.3028(18)	N(6)-C(5)-S(10)	113.66(10)
N(6)-C(7)	1.4724(17)	N(4)-C(5)-S(10)	120.38(10)
N(4)-H(4)	0.863(15)	N(6)-C(5)-N(4)	125.96(12)
N(6)-H(6)	0.874(15)	C(5)-N(6)-C(7)	127.05(11)
S(10)-O(11)	1.4811(13)	N(6)-C(5)-S(10)-O(11)	5.4178
S(10)-O(12)	1.4881(11)	N(6)-C(5)-S(10)-O(12)	109.2723
		N(4)-C(5)-S(10)-O(11)	174.0418
		N(4)-C(5)-S(10)-O(12)	71.2681

Table 7. X-ray crystallographic data of *N,N'*-diisopropylthiourea dioxide 25

The S-O(11) bond lies in the plane of the amidine moiety and forms an intramolecular hydrogen bond with N-H(6) as shown in Figure 13. This NH and SO are also involved in a reciprocal dimer formation with the same groups in another molecule. This is shown in Figure 13.

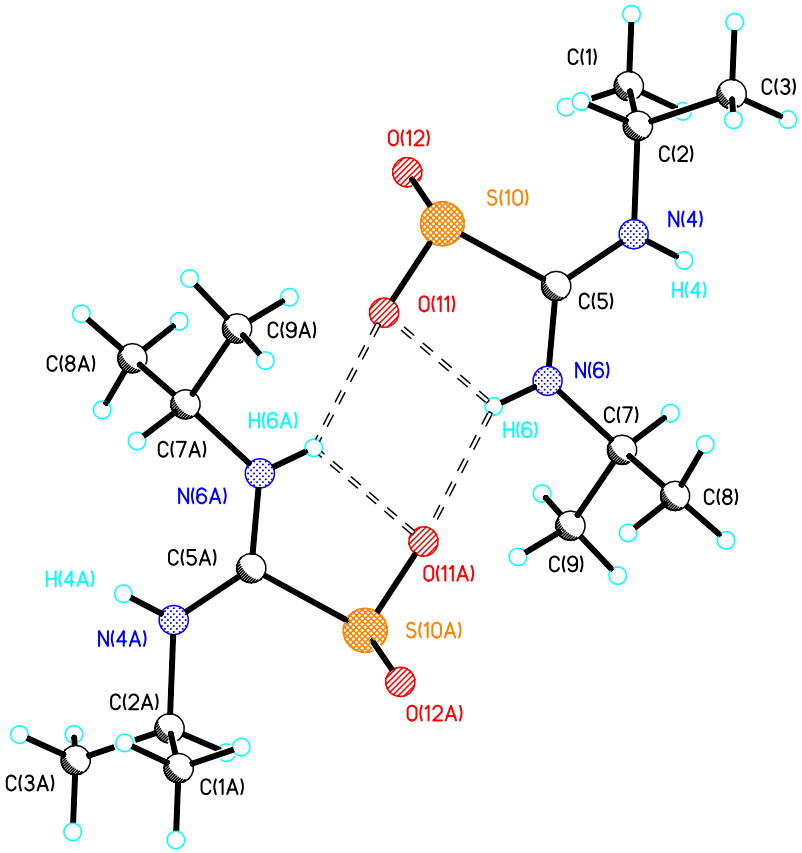


Figure 13. Dioxide 25 showing dimer formation

The intramolecular hydrogen bonding, at 2.127 Å, found in the X-ray structure of dioxide **25** also explains why there are two sets of methyl and methine environments in the NMR spectrum.

The other N-H(4) and S-O(12) groups are involved in an infinite zigzag hydrogen-bonded chain as shown in Figure 14.

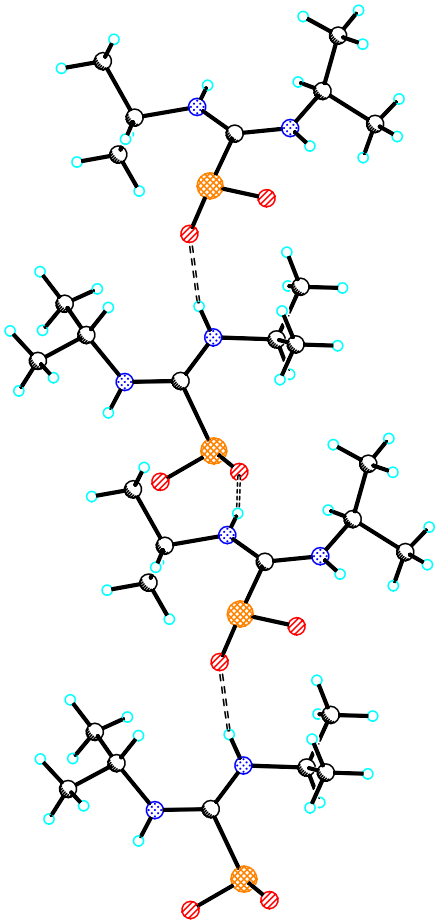
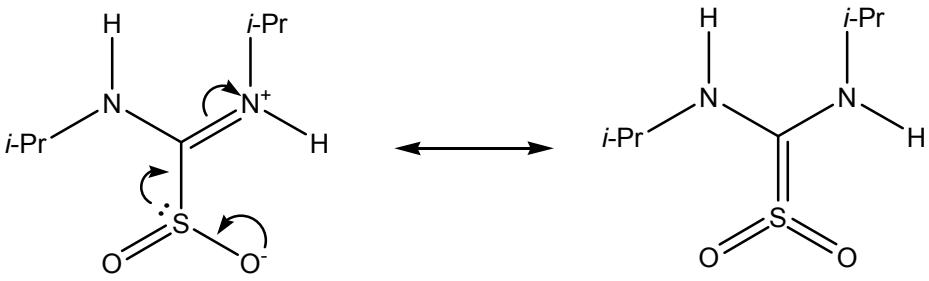


Figure 14. Zigzag intermolecular hydrogen bonding of dioxide 25

It could be argued that the dioxide **25** adopts a planar geometry at the sulfur atom which is similar in structure to sulfenes.



Scheme 37. Sulfene resonance form of dioxide 25

However, the contribution of sulfene geometry in dioxide **25** is probably non-existent. The X-ray crystal structure of the dioxide **25** was found to be pyramidal C_1 at the sulfur atom. The C-S bond length 1.9045 Å is considerably longer than a typical C=S double bond, estimated at 1.62 Å.[11] The planar amidine functionality (sp^2 cationic iminium-nitrogen compared with sp^3 neutral-nitrogen) and the pyramidal sulfinate group supports the proposal from published work that thiourea dioxides adopt a zwitterionic structure.[38]

N,N'-Diisopropylthiourea dioxide is water soluble and has improved solubility in alcoholic solvents when compared with the parent dioxide. The synthesis was only carried out up to *ca.* 13 mmol scale so as to avoid using too much aqueous hydrogen peroxide and therefore make filtration of the dioxide more difficult. The oxidation of *N,N'*-diisopropylthiourea under non-aqueous conditions is described in chapter 5. The dioxide consistently tested positive for dithionite ions, can be detected with soft mass spectrometry techniques *e.g.* electrospray ionisation and is stable in air and in solution for a few days. If stored at room temperature in the dark and away from moisture, the dioxide was found to remain unchanged for at least 2 months.

The trace quantity of *N,N'*-diisopropylthiourea trioxide **27** isolated was fully characterised. It was found to have a higher melting point than the dioxide **25** and from NMR spectroscopic studies, appears to retain the intramolecular hydrogen bonding described for the dioxide. The trioxide is water soluble and tested negative for dithionite ions. The asymmetric and symmetric sulfonate stretching modes of the trioxide **27** located at 1231 and 1051 cm^{-1} respectively, are distinguishable from the sulfinate modes of the dioxide **25** found at 1080 and 1009 cm^{-1} respectively, which overall, is in agreement with work by Walter (Table 4, 2.1.1).[53, 110]

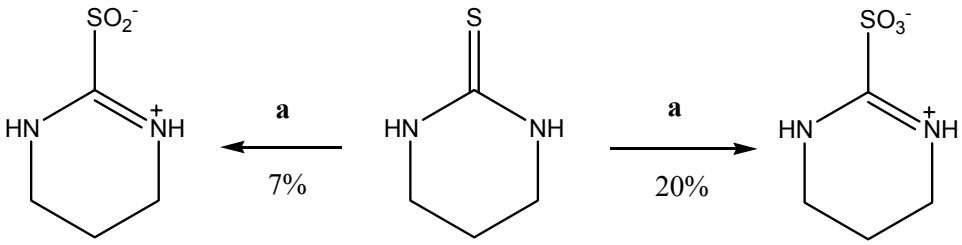
N,N'-Diisopropylthiourea dioxide **25** was predicted to be isolable based on the relatively short C-S bond length, deduced from DFT calculations. The calculations revealed the presence of an intramolecular hydrogen bond. The synthesis of the dioxide **25** was

successfully carried out, at high yield, with hydrogen peroxide and a molybdate catalyst. The NMR spectra of the dioxide revealed the presence of two magnetically non-equivalent isopropyl groups. The observations by NMR were supported by the computational and X-ray crystallographic data and thought to be characteristic of an intramolecular hydrogen bond.

2.3.2 Dioxide and trioxide of propylenethiourea

Propylenethiourea dioxide **26** was synthesised under catalytic conditions in *ca.* 7% yield; it was more difficult to isolate than *N,N'*-diisopropylthiourea dioxide **25**. The new dioxide **26** is water soluble and partially soluble in chlorinated solvents, in particular chloroform. It repeatedly tested positive for dithionite ions and was found to remain unchanged in deuterium oxide for 3 days as shown from NMR experiments.

The low yield was thought to be due to the rapid formation of propylenethiourea trioxide **28** (Scheme 38) and after repeated attempts, trioxide **28** was isolated with the aid of flash chromatography. An improved synthesis of propylenethiourea dioxide under non-aqueous conditions is outlined in chapter 5.



26 **28**

a: 2 equiv. H_2O_2, $MoO_2(acac)_2$, 1,4-dioxane, Et_2O

Scheme 38. Catalytic oxidation of propylenethiourea with hydrogen peroxide

The computational structure of propylenethiourea dioxide possessed intramolecular hydrogen bonding but this could not be observed with NMR studies.

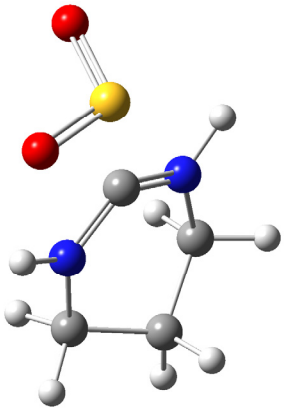


Figure 15. Computational structure of propylenethiourea dioxide 26

We have not been able to obtain crystals of **26** of sufficient quality for X-ray crystallographic studies.

As expected, the asymmetric and symmetric sulfonate stretching modes of the trioxide **28** were located at 1229 and 1040 cm^{-1}, respectively; the corresponding sulfinate modes of the dioxide **26** were found at 1094 and 989 cm^{-1}.[53, 110]

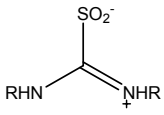
The computational predictions have so far successfully predicted that *N,N'*-diisopropylthiourea dioxide and propylenethiourea dioxide are isolable. We therefore directed our attention to the synthetically more problematic *N,N'*-diarylthiourea dioxides, with particular attention given to applying the computational models developed so far.

2.4 *N,N'*-Diarylthiourea dioxides

Calculations were carried out on a range of derivatives of *N,N'*-diphenylthiourea dioxide **19** in order to identify trends which could lead to the identification of isolable derivatives. A series of compounds containing electron-donating and -withdrawing groups was investigated and key data are summarised in Table 8.

The computational studies were carried out with 6-31G(d,p) basis set in the gas phase (instead of 6-311+G(3d,p) in water) so that the series could accommodate potentially

larger molecules in which the optimisations would converge in reasonable time (*ca.* 5 days). Thiourea dioxide **3** and *N,N'*-diisopropylthiourea dioxide **25** were also calculated at the same level in order to establish a reliable benchmark. It was decided that compounds with C-S bonds which were predicted longer, *i.e.* weaker, than *N,N'*-diphenylthiourea dioxide would be unsuitable targets. Compounds with C-S bond lengths similar to thiourea dioxide and *N,N'*-diisopropylthiourea dioxide were considered isolable.



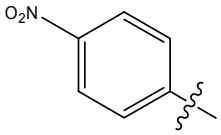
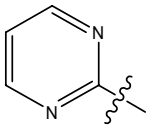
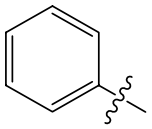
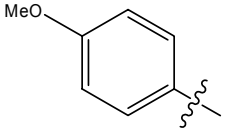
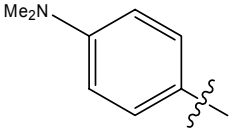
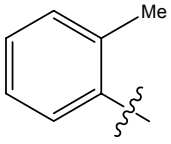
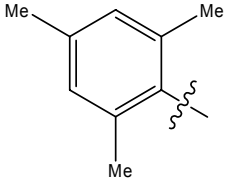
	R	C-S /Å	O-HN /Å
1		2.28038	1.75243
2		2.20197	1.77668
3		2.17512	1.75301
4		2.15321	1.77285
5		2.11013	1.76465
6		2.08625	1.78247
7		2.02106	1.80324
8		2.04329	1.80486
9	H	2.01849	1.93878

Table 8. Calculated geometries of thiourea dioxide derivatives

All of the analogues listed in Table 8 possess intramolecular hydrogen bonding, as described previously. The computational data show a marked trend with regard to the electronic factors affecting the C-S bond length. Steric factors are also thought to influence the C-S bond length.

The electron-poor derivatives, such as *N,N'*-di-*p*-nitrophenylthiourea dioxide (entry 1, Table 8), were predicted to have longer C-S bond lengths than the diphenyl derivative (entry 3). In contrast, electron-rich derivatives, such as the 1,3-bis(*p-N,N'*-dimethylaminophenyl)thiourea dioxide (entry 5), were predicted to have shorter C-S bond lengths. Both nitro- and dimethylamino-derivatives have similar conformation *i.e.* similar overlap of the aromatic and amidine π-system, as shown in Figures 16 and 17. In addition, both analogues were predicted to have significantly different C-S bond lengths. Therefore, it appears that electronic factors influence the C-S bond in diaryl derivatives.

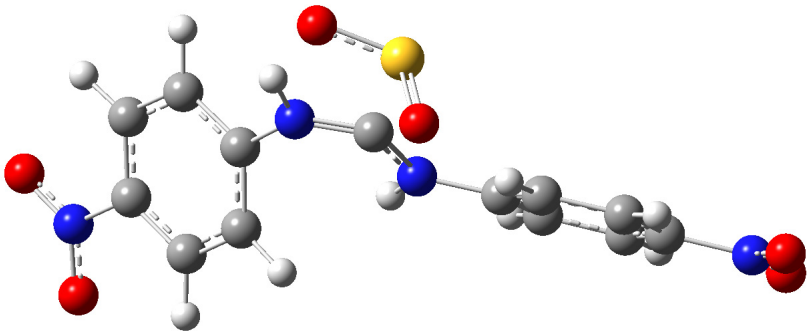


Figure 16. DFT predicted structure of *N,N'*-di-*p*-nitrophenylthiourea dioxide

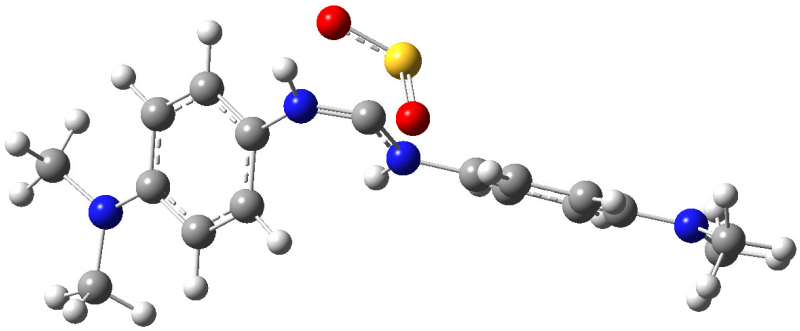


Figure 17. DFT predicted structure of 1,3-bis(*p*-*N,N'*-dimethylaminophenyl)thiourea dioxide

However, close inspection of the conformation of the predicted structures listed in Table 8 reveals that not all aromatic rings are coplanar with the amidine moiety. Only the pyrimidinyl analogue (entry 2) resulted in a conformer where both aromatic rings were co-planar with the amidine moiety (Figure 18).

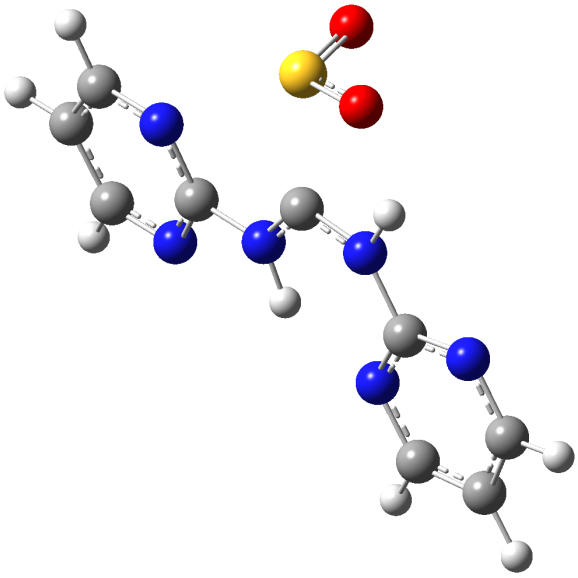


Figure 18. DFT predicted structure of *N,N'*-di(2-pyrimidinyl)thiourea dioxide

The degree of overlap of the π-systems was greatly diminished when methyl groups were incorporated at the *ortho*-positions of the aniline ring. For example, *N,N'*-di-*o*-tolylthiourea dioxide (entry 6) was predicted to have a shorter C-S bond length 2.08625 Å compared with the diphenyl derivative 2.17512 Å. *N,N'*-Dimesitylthiourea dioxide (entry 7) is predicted to have the shortest C-S bond 2.02106 Å, second only to thiourea dioxide (entry 9) 2.01849 Å.

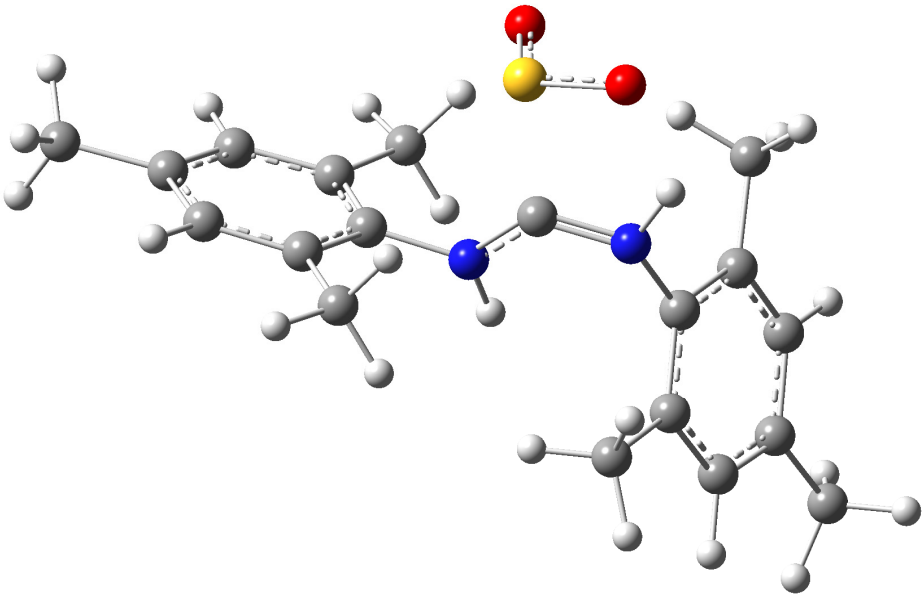


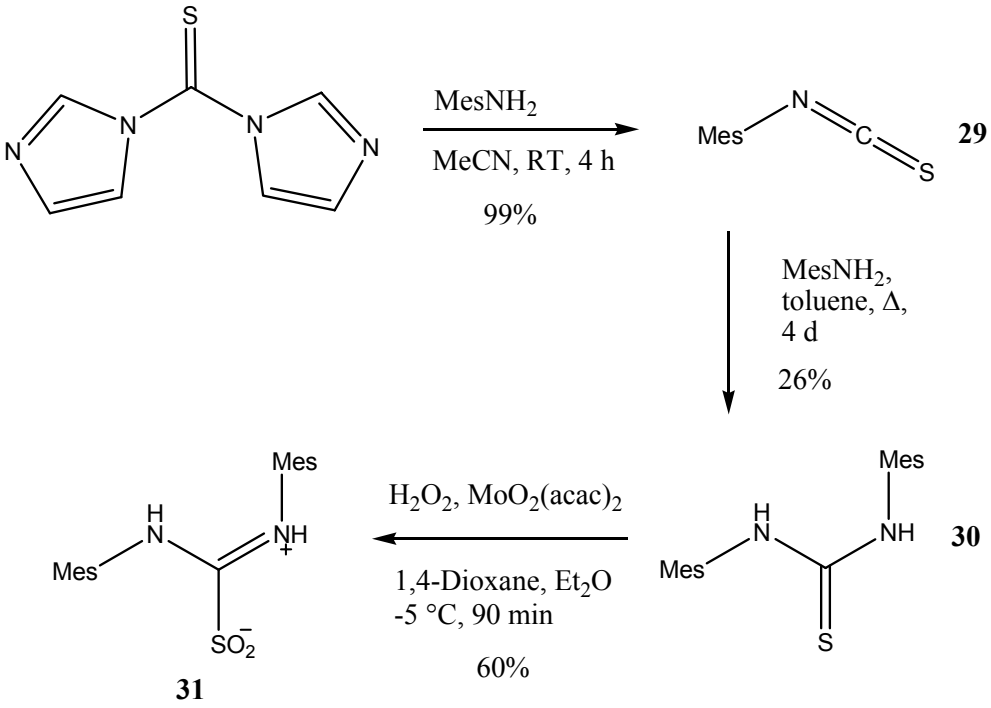
Figure 19. DFT predicted structure of *N,N'*-dimesitylthiourea dioxide 31

The computational structure of *N,N'*-dimesitylthiourea dioxide **31** (Figure 19) demonstrated that the aromatic rings are not coplanar with the amidine moiety. Therefore, the aromatic π-system would appear to have little influence on the C-S bond. From our calculations, the diminished overlap of the aromatic ring π-system with the amidine π-system, probably due to steric repulsion, leads to dioxide analogues with shorter C-S bonds.

Overall, the computational data show that electronic and steric factors are involved in affecting the C-S bond length. From the data in Table 8, *N,N'*-dimesitylthiourea dioxide

was predicted to have the shortest C-S bond of the diaryl analogues and was therefore chosen as our next target.

The synthesis of *N,N'*-dimesitylthiourea dioxide **31** was successfully carried out as outlined in Scheme 39. The thiourea **30**, synthesised from the isothiocyanate **29**, was obtained following literature procedures using commercially available starting materials.[128] The dioxide **31** was then isolated *via* the catalytic oxidation of the thiourea with hydrogen peroxide.



Scheme 39. Synthesis of *N,N'*-dimesitylthiourea dioxide 31

N,N'-Dimesitylthiourea dioxide is insoluble in water and chlorinated solvents, and gives the characteristic sulfinate asymmetric and symmetric stretching modes at 1104 and 1008 cm^{-1}, respectively. The compound was incompatible with the dithionite test because it was insoluble in water and therefore tested negative for dithionite ions. The dioxide was found to be air stable for at least a few days but can be stored at room temperature, in the dark and away from moisture for *ca.* 3 months. NMR spectroscopic analysis revealed the

presence of apparent intramolecular hydrogen bonding as evident from the two sets of *ortho*-methyl and *para*-methyl signals. The dioxide did not give a satisfactory elemental analysis (C: 65.32, H: 7.01, N: 7.99, S: 8.20%; theoretical composition C: 66.25, H: 7.02, N: 8.13, S: 9.31%) but was detected with high resolution LSIMS.

To conclude, it appears that *N,N'*-disubstituted thiourea dioxides are difficult to isolate. The structure of *N,N'*-diisopropylthiourea dioxide in the solid state and solution appears to demonstrate the contribution of intramolecular hydrogen bonding to the structure and probable stability of *N,N*'-disubstituted thiourea dioxides. The synthesis of cyclic thiourea dioxides with aqueous hydrogen peroxide proved more difficult. The three novel thiourea dioxides isolated in this work are air stable and the procedure for their syntheses was successfully repeated. An improved synthesis of the thiourea dioxides under non-aqueous conditions is outlined in chapter 5.

Characterisation has focused heavily on IR and elemental analyses, both techniques of which require sufficiently pure samples. Attempts to obtain ^{33}S NMR spectroscopic data for all the dioxides gave very broad signals (due to the asymmetry of the sulfur centre in the dioxides) and could not be interpreted. The dithionite test has proved useful in identifying most of the dioxides generated *in situ* but is dependent on the water solubility of the dioxide.

Problems with characterisation are further amplified by the fact that the corresponding trioxide has been detected, especially for the cyclic derivatives, even when two equivalents of oxidising agent are used. The formation of the trioxide is probably due to oxidation of the dioxide or by other mechanisms *e.g.* disproportionation[129, 130] which are observed in other *S,S*-dioxides (sulfinic acids).

There does, however, appear to be good agreement with computational predictions and synthetic work. The stability of the dioxides is largely influenced by the C-S bond length.

It is noted however that the calculations have not been developed to account for other factors which affect the decomposition of the dioxides.

2.5 Future work

The isolation of thiourea dioxide derivatives was thought to be difficult mainly because of the water solubility and consequent isolation. Alternative oxaziridine oxidants were found to be suitable oxidising agents and are discussed in chapter 5.

Purification *via* methods that do not involve chromatography are seldom quoted in the literature.[66] For example, the dioxides isolated to date appeared stable on TLC plates but decomposed under flash chromatography with untreated silica. Neither the use of neutralised silica, for example silica washed with triethylamine/diethyl ether, nor other stationary phases were investigated. A range of methods could be investigated so that mixtures of oxyacids of thiourea, repeatedly encountered in this area, are separated without detrimental breakdown.

The isolation of bulky diarylthiourea dioxides was of interest and could be developed further. In particular, it was thought that a series of aryl derivatives bearing both electron-withdrawing and electron-donating groups could prove interesting and influence the reactivity of the dioxides.

The observations presented in this chapter have centred on symmetrical thiourea dioxide derivatives. The next logical step would be the investigation of asymmetric thiourea dioxide derivatives. The exploration of combinations of stable and relatively less stable functionality could be of potential significance.

Chapter 3. Investigation into the application of thiourea dioxide derivatives

As mentioned previously, thiourea dioxide is well known as a reducing agent but the nature of the decomposition species is still a matter of debate. There are reports that describe thiourea dioxide as a precursor to the sulfinate dianion[35] SO_2^{2-} and the radical anion[35, 75] $SO_2^{\cdot-}$, both of which are powerful reducing species. It was envisaged that the weaker C-S bond in *N,N'*-diisopropylthiourea dioxide (+0.0453 Å *cf.* thiourea dioxide, see 2.3.1) would lead to an accelerated generation of the reducing species compared with the parent dioxide. A series of substrates were therefore chosen to test this hypothesis.

The reduction of aldehydes,[82] ketones[78-80] and disulfides[83] with thiourea dioxide is well documented and were chosen as substrates for comparing the reducing ability of thiourea dioxide with *N,N'*-diisopropylthiourea dioxide. The reduction of sulfimides[83] was also of interest and is discussed in detail in chapter 4.

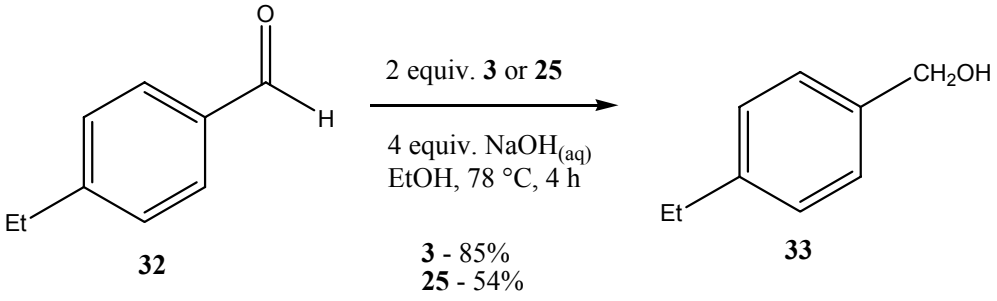
The formation of radical anions from thiourea dioxide has been applied to polymerisation initiation reactions[105] and transition metal reductions.[39, 76, 77] Interestingly, work which investigates the application of SET reactions from thiourea dioxide (*cf.* samarium diiodide)[131] has not been reported as frequently. Therefore, in addition to discovering why the radical anion has not been utilised as much and also to determine if the novel dioxide **25** would prove the better precursor, it seemed logical to investigate a series of experiments which are thought to take place *via* SET processes. The removal of tosyl groups from *N*-tosylaziridines[132, 133] (3.4.1) and the deprotection of CBz-amines[134] (3.4.3), all of which are known to occur with SET reagents, were therefore chosen to investigate the utility of thiourea dioxides. The reduction of nitriles with SET reagents, such as samarium diiodide, is more challenging.[131] Nitriles were therefore investigated in order

to probe the reducing ability of the derivatives of thiourea dioxide and are described in 3.4.2.

The formation of sulfones from sodium hydroxymethanesulfinate and alkyl halides is known and thought to involve the sulfinate dianion.[135] The potential of *N,N'*-diisopropylthiourea dioxide **25** to act as a precursor to the dianion was thought to provide an opportunity to not only determine if sulfones could be prepared in this way but also to yield more mechanistic evidence with regard to the nature of the decomposition products of **25** and consequently, thiourea dioxide.

3.1 Reduction of aldehydes and ketones

4-Ethylbenzaldehyde **32** was successfully reduced to 4-ethylbenzylalcohol **33** with two equivalents of the thiourea dioxide **3** in sodium hydroxide (Scheme 40).

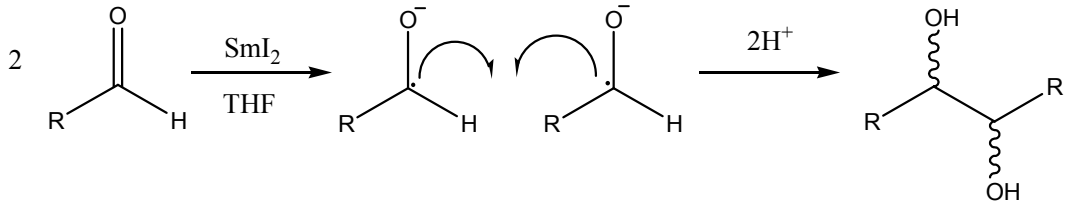


32 **33**

Scheme 40. Reduction of 4-ethylbenzaldehyde

Pleasingly, *N,N'*-diisopropylthiourea dioxide **25** also reduced aldehyde **32**. However, thiourea dioxide (85%) appeared to be a higher yielding reducing agent for the aldehyde than *N,N*'-diisopropylthiourea dioxide under these conditions. Therefore, the reduction of aldehydes was not pursued further.

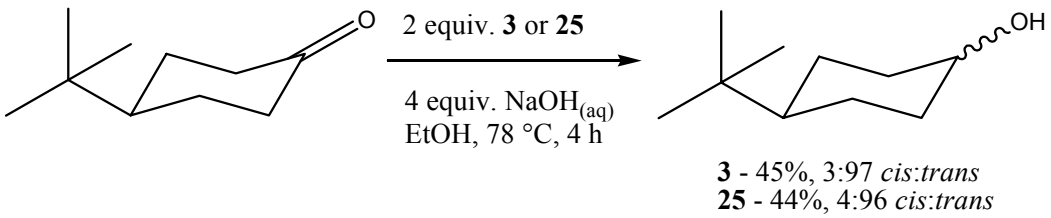
Kagan and co-workers have demonstrated that the reduction of aldehydes with samarium diiodide in THF can lead to the formation of pinacols, as shown by the dimerisation of two ketyl radicals (Scheme 41).[136]



Scheme 41. Pinacol formation[136] from SET reduction of aldehydes

It was envisaged that the generation of radical anion reducing species from thiourea dioxide derivatives could also be utilised in the formation of pinacols from aldehydes or ketones. Consequently, *N,N'*-diisopropylthiourea dioxide in tetrahydrofuran was investigated as a reducing agent for the formation of the corresponding pinacols from aldehyde **32**. Unfortunately, no pinacol products could be detected. The reaction mixture was composed of *N,N'*-diisopropylurea, starting aldehyde and unknown compounds as judged by NMR spectroscopy. *N,N'*-Diisopropylurea was thought to be formed from the nucleophilic substitution of *N,N*'-diisopropylthiourea dioxide with sodium hydroxide (see chapter 4). A more detailed discussion about the mechanism of the reduction of carbonyl groups with thiourea dioxide derivatives is provided in 4.2.

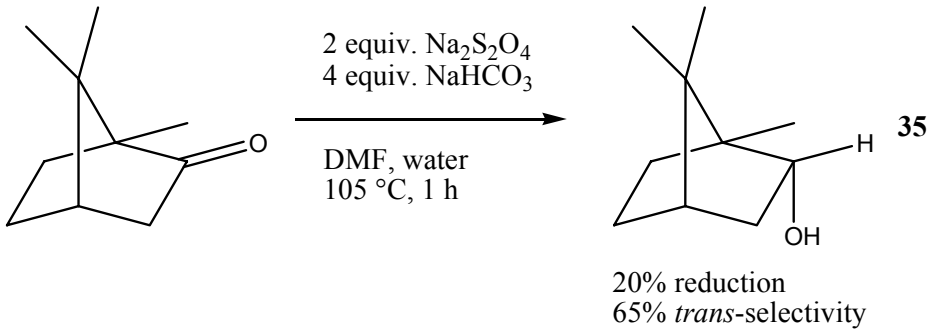
The reduction of ketones was also investigated, in particular with a view to investigating the stereoselectivity. 4-*tert*-Butylcyclohexanone was reduced to a mixture of the *cis*-(**34a**) and *trans*-4-*tert*-butylcyclohexanol (**34b**) with thiourea dioxide **3** and *N,N*'-diisopropylthiourea dioxide **25** under the same conditions for the reduction of 4-ethylbenzaldehyde (Scheme 42). Both dioxides gave similar yields and diastereomeric ratios (as deduced from NMR spectroscopic data) of the alcohol.



Scheme 42. Reduction of 4-*tert*-butylcyclohexanone

It was reported that the reduction of cholestan-3-one in alcoholic potassium hydroxide operated *via* a Meerwein-Ponndorf mechanism and that the corresponding cholestan-3-ols were formed in quantitative yields with or without thiourea dioxide.[79] In the same paper, it was found that cyclohexanone could be reduced in the absence of thiourea dioxide 'to a comparable degree (GLC)' to when thiourea dioxide was used, the latter observation referring to work by other authors. They did not supply any conversion data. In our work, only the starting ketone could be detected in the crude mixtures when either sodium hydroxide or *N,N'*-diisopropylthiourea dioxide **25** were omitted. In our hands, the reduction of 4-*tert*-butylcyclohexanone does require both dioxide **25** and sodium hydroxide.

1S-(-)-Camphor was considered the more challenging of the carbonyl series and can be reduced under metal-ammonia conditions, as demonstrated by Murphy[137] and Charles.[138] In particular, Krapcho and Seidman reported that sodium dithionite in DMF reduced *1S*-(-)-camphor to borneol **35** (*trans*- or endo-alcohol) at 20% yield.[101] The authors found that the dithionite reduction gave stereoselectivity similar to that of lithium-ammonia conditions (% *trans*-alcohol: dithionite 65; $NaBH_4$ 24; Li/NH_3 90), that is the reduction proceeded through a radical anion pathway.



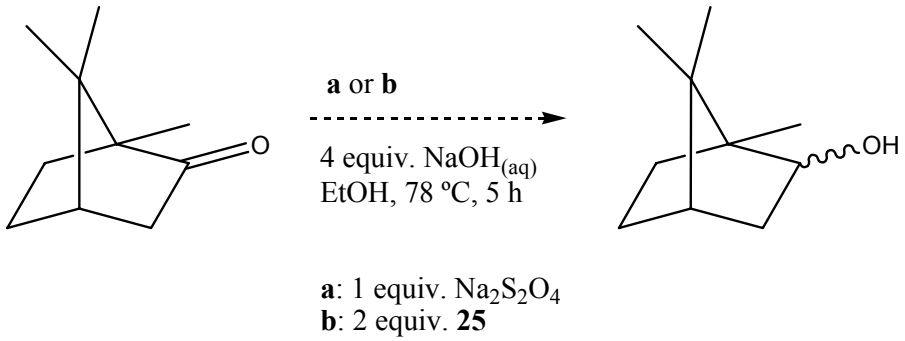
Scheme 43. Reduction[101] of *1S*-(-)-camphor to borneol

Sodium dithionite $Na_2S_2O_4$ is known to dissociate homolytically to two radical anions.[139, 140]

$$S_2O_4^{2-} \rightleftharpoons 2\ SO_2^{\bullet -}$$

It was of interest to discover if camphor can be reduced under milder conditions with *N,N'*-diisopropylthiourea dioxide, also thought to be a $SO_2^{\bullet -}$ precursor. The reactions were carried out comparing sodium dithionite to *N,N'*-diisopropylthiourea dioxide.

One mole of thiourea dioxide at high pH is thought to yield 1 mole of the radical anion (mechanism discussed in chapter 4). Therefore reduction of camphor was compared using either one equivalent of sodium dithionite or two equivalents of *N,N'*-diisopropylthiourea dioxide **25** (Scheme 44).



Scheme 44. Reduction of *1S*-(-)-camphor

Sodium dithionite was ineffective at reducing camphor under our milder conditions, in contrast to the conditions employed by Krapcho and Seidman.[101] A 72% recovery of the starting ketone was achieved after flash chromatography. Similarly, when *N,N'*-diisopropylthiourea dioxide **25** was used, the crude reaction mixture was found to contain the starting ketone and *N,N'*-diisopropylurea. No subsequent purification was carried out.

From the reductions of carbonyl compounds, it appears that *N,N'*-diisopropylthiourea dioxide **25** has comparable reducing properties to the parent dioxide **3**.

3.2 Reduction of nitrogen-containing functional groups

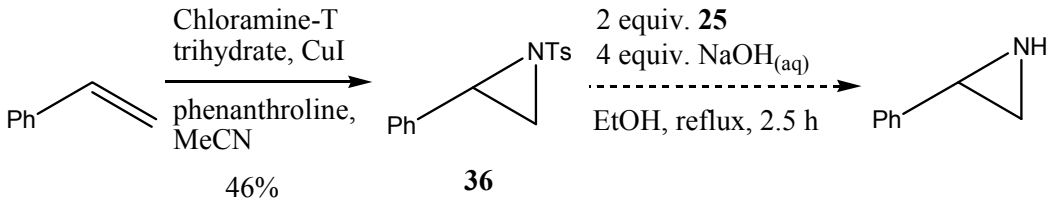
Thiourea dioxide is known to reduce nitro groups to amines[86, 87] and azo groups to the corresponding hydrazo groups.[87] However the reduction of other functional groups such as nitriles and protecting groups (arylsulfonyl and *N*-CBz groups) has not been studied.

In view of the anticipated higher reducing power from *N,N'*-diisopropylthiourea dioxide **25** as compared with thiourea dioxide, it was of interest to discover if the aforementioned functional groups, unexplored to date, could be reduced with the new dioxide **25**. All reduced products that were anticipated from the following reactions are isolable literature compounds.

3.2.1 Removal of tosyl groups from *N*-tosylaziridines

Arylsulfonyl substituents are effective protecting groups for amines though removal is troublesome. They have been removed *via* reductive methods including sonication in magnesium-methanol,[133] sodium in liquid ammonia and strong acids.[132] Consequently it was envisaged that the thiourea dioxides in sodium hydroxide may provide a milder alternative.

The chosen substrate, 2-phenyl-*N*-tosylaziridine **36** was prepared from styrene using procedures developed in our group and is outlined in Scheme 45.



Scheme 45. Synthesis of *N*-tosylaziridine 36 and subsequent deprotection

A reaction between *N*-tosylaziridine **36** and *N,N'*-diisopropylthiourea dioxide **25** in sodium hydroxide was carried out with a view to removing the tosyl group to give 2-phenylaziridine. After dioxide **25** was consumed (judged by TLC) at 2½ hours, the reaction gave a complex mixture of the starting tosylaziridine and unknown material.

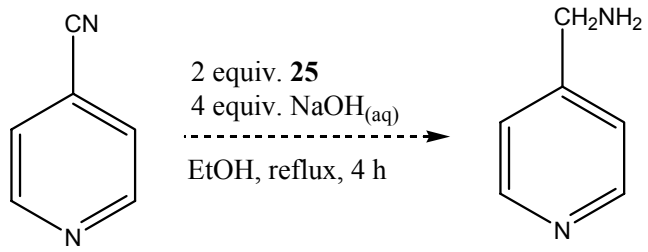
The experiments were repeated without **25** to test the effect of sodium hydroxide/ethoxide nucleophilic ring opening. After flash chromatography, a mixture of products which gave complex NMR spectra was obtained. GCMS (EI/CI) analysis of the mixtures was inconclusive.

The results suggest that *N,N'*-diisopropylthiourea dioxide was an ineffective reducing agent under these conditions for the removal of tosyl groups. Further investigations into the reduction of *N*-tosylaziridines were ceased.

3.2.2 Reduction of nitriles to primary amines

There are several reports that describe the reduction of nitriles to primary amines, for example, *via* catalytic hydrogenation[141] and transition metal assisted borohydride reductions. Caddick and co-workers described the reduction of a range of alkyl and aryl nitriles with catalytic quantities of nickel(II)chloride with excess sodium borohydride.[142]

An electron-poor nitrile, 4-pyridinecarbonitrile **37** was reacted with dioxide **25** in sodium hydroxide to investigate if nitriles are reducible by thiourea dioxides.



37

Scheme 46. Reduction of 4-pyridinecarbonitrile

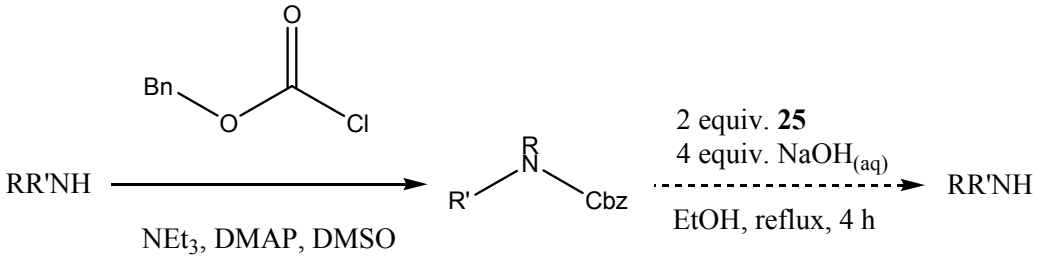
Unfortunately, the corresponding amine could not be detected in the crude reaction mixture. Only *N,N'*-diisopropylurea and the starting nitrile were detected in the product mixture as judged by NMR spectroscopy.

As a result of our observations outlined so far, the reduction of other substrates *e.g.* alkynes[143] and alkenes of α,β-unsaturated-γ-dicarbonyl compounds,[144] were not considered high priority at the time and therefore not investigated.

3.2.3 Deprotection of CBz-amines

The removal of CBz or Z groups from the respective protected amines has been widely explored. Published procedures include acid catalysis,[145] hydrogenation[146] and dissolving metal reductions.[134] It was thus envisaged that thiourea dioxide derivatives may serve as alternatives to the established procedures.

Benzylamine and piperidine were protected with the CBz group (Scheme 47) and then reacted with *N,N'*-diisopropylthiourea dioxide **25** in sodium hydroxide. The reactions were monitored by GC with 1,3,5-tri-*tert*-butylbenzene as the internal standard. The protected CBz-amines, **38** and **39**, were found to withstand the GC conditions and none of the corresponding amine was detected.



38: R = H, R' = Bn (25%)
39: R, R' = -$(CH_2)_2NH(CH_2)_2$- (52%)

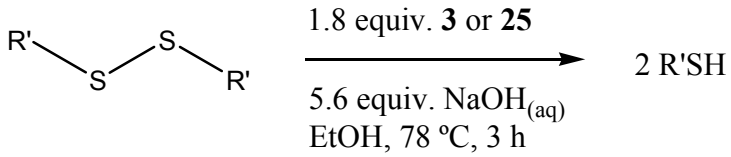
Scheme 47. Synthesis and deprotection of CBz-amines

Of the two analogues tested, only *O,N*-dibenzylcarbamate (**38**, R = H; R' = Bn, Scheme 47) was found to reduce to benzylamine, as evident from the 2.7% conversion. *N*-Carboxybenzylpiperidine **39** was not found to reduce at all.

3.3 Reduction of disulfides

The reduction of disulfides with thiourea dioxide was investigated by others under phase-transfer conditions.[83, 85] Homogeneous conditions have not been investigated presumably

because thiourea dioxide is poorly soluble in organic solvents. As mentioned in chapter 2, the isopropyl analogue **25** has a higher solubility in alcoholic solvent compared with thiourea dioxide **3**. Therefore, it was of interest to discover if the improved solubility could be utilised in the reduction of disulfides under simpler, homogeneous conditions. It turned out that *S,S'*-diphenyldisulfide and *S,S'*-dibenzyldisulfide were successfully reduced to their corresponding thiols (**40** and **41**, respectively) in good yields with thiourea dioxide **3** and *N,N'*-diisopropylthiourea dioxide **25**, without the need for phase transfer catalysts.



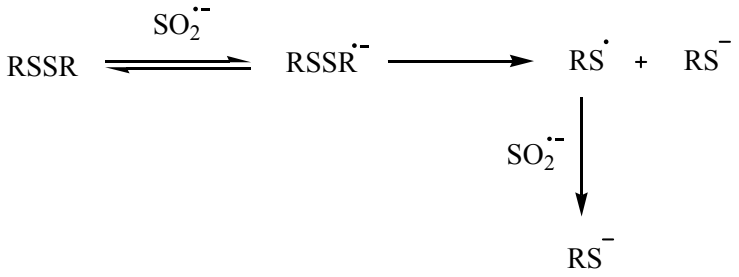
Scheme 48. Reduction of disulfides

	Thiol % yield	
Dioxide	**40, R' = Ph**	**41, R' = Bn**
3	53	48
25	86	68

Table 9. Thiols from disulfides

The data were very encouraging, demonstrating in this case that *N,N'*-diisopropylthiourea dioxide was a more effective reducing agent than thiourea dioxide.

The mechanism of reduction of disulfides to thiolates was thought to proceed *via* a SET process.[147] The thiolate ions could then be isolated upon protonation with ethanol.



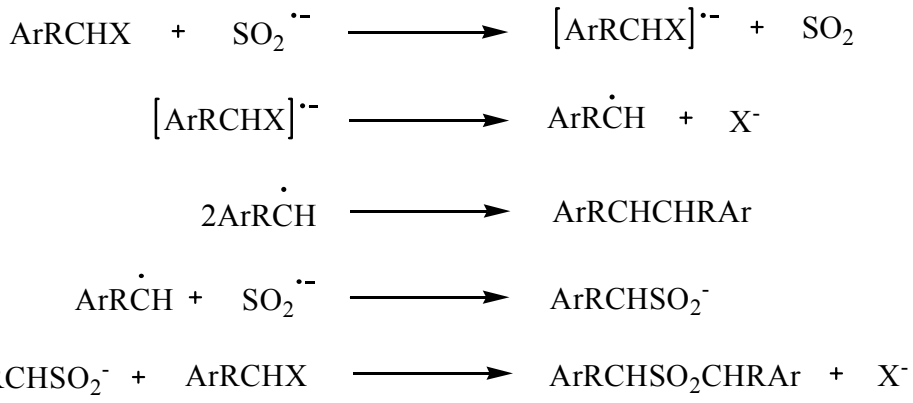
Scheme 49. Mechanism of the reduction of disulfides

The nature of the reducing species is discussed in more detail in chapter 4.

3.4 Reduction of alkyl halides

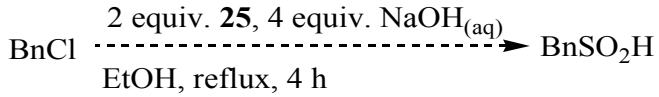
Khurana and co-workers provided an interesting account of the reductive coupling of benzylic halides with sodium dithionite.[148] They observed that primary alkyl halides in the presence of sodium dithionite in DMF or HMPA gave mixtures of dimers and sulfones.

Khurana proposed that $SO_2^{\bullet-}$, generated from sodium dithionite, reacts with benzylic halides according to Scheme 50.



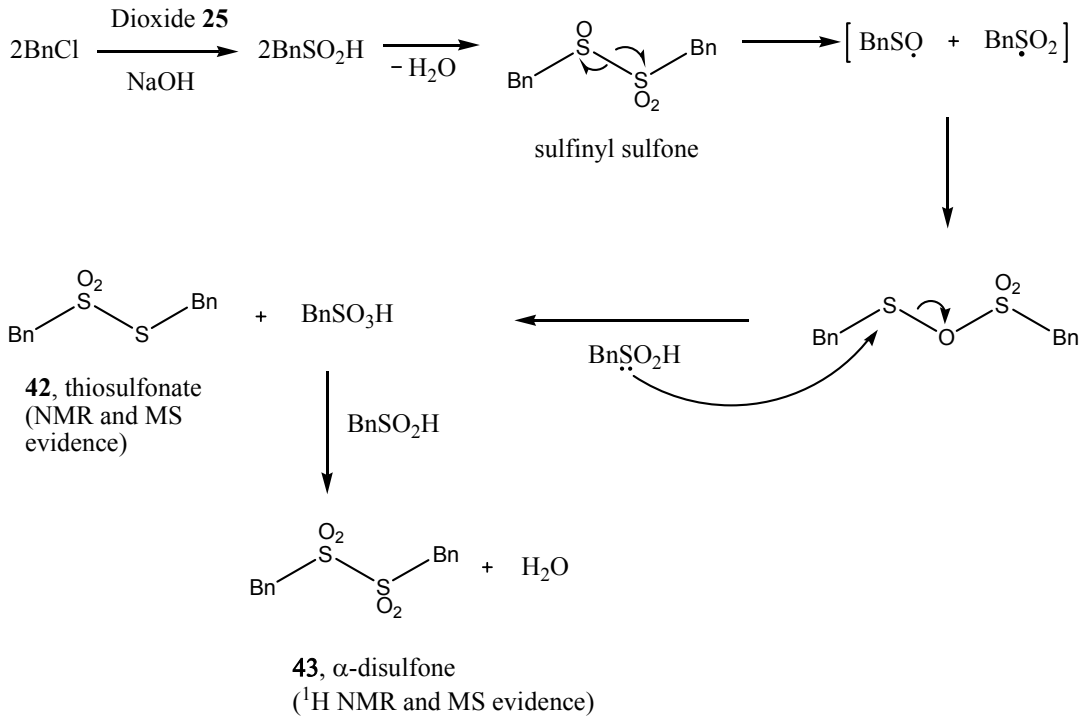
Scheme 50. Formation of dibenzyl dimers and sulfones from benzyl halides[148]

Given that the radical anion $SO_2^{\cdot-}$ is also generated from the decomposition of thiourea dioxide,[35, 75] it was of interest to investigate the product distribution of a similar reaction *e.g. N,N'*-diisopropylthiourea dioxide **25** and benzyl chloride (Scheme 51).



Scheme 51. Reaction of benzyl chloride with *N,N'*-diisopropylthiourea dioxide 25

The reaction mixture was purified using flash chromatography and no benzyl alcohol, as expected from the nucleophilic substitution between sodium hydroxide and benzyl chloride, was detected. The individual fractions were composed of a mixture of a thiosulfonate **42** and an α-disulfone **43**, and was thought to form *via* the disproportionation of benzylsulfinic acid as determined from NMR spectroscopic and mass spectrometry analyses. A detailed report on the complex mechanism of sulfinic acid disproportionation was provided by Kice and formed the basis of the outline provided in Scheme 52.[129, 130] Neither dibenzyl or dibenzylsulfone, in accordance with Khurana's observations, were detected. Benzylsulfinic acid, which could not be isolated, was thought to form *in situ* analogously to Khurana's mechanism (Scheme 50).



Scheme 52. Disproportionation[129, 130] of benzylsulfinic acid

Overall, it appears that *N,N'*-diisopropylthiourea dioxide at high pH yields a sulfur containing fragment, probably $SO_2^{\cdot-}$, which reacts with benzyl chloride to give benzylsulfinic acid. Under our conditions, benzylsulfinic acid (S = +2) then reacts with itself to give a disproportionation product, the sulfinyl sulfone $BnS(O)SO_2Bn$ (S = +1 and +3). The sulfinyl sulfone was then thought to react further *via* a pathway, analogous to the mechanism outlined by Kice, to give two products **42** and **43**, which were identified spectroscopically.

To conclude this chapter, good yields were achieved with the reduction of carbonyl-containing compounds with the novel dioxide **25**. The reduction of disulfides was very encouraging and under simpler reaction conditions was substantially improved with the dioxide **25**. The improved reductions were thought to be due to the higher solubility and the higher reactivity (as shown from the longer C-S bond) of the dioxide **25** compared with thiourea dioxide.

The reduction of other nitrogen-containing functional groups outlined in 3.4.1 – 3.4.3 were found to be too challenging.

The formation of benzylsulfinic acid was explained by the reaction of benzylchloride with a sulfur containing anion, of which there are two potential species. When taking into consideration of Khurana's data,[148] our observations reveal that the formation of $SO_2^{\cdot-}$ from *N,N'*-diisopropylthiourea dioxide at high pH, is likely. Alternatively, it could be envisaged that a potential dianion SO_2^{2-} (mentioned in the chapter introduction) is formed[35, 49] and then reacts with benzyl chloride *via* a nucleophilic substitution mechanism to afford benzylsulfinic acid. In light of the high reactivity and potentially complex reaction pathways of sulfinic acids,[130] the reduction of alkyl halides was thought to be unsuitable for our mechanistic studies, with respect to the decomposition of thiourea dioxides. In the next chapter, sulfimides are employed as more useful substrates, in order to develop the present understanding about the mechanism of decomposition of thiourea dioxides.

3.5 Future work

The advances made in the reduction of disulfides (and sulfimides described in the next chapter) investigated were very encouraging. The utility of substituted thiourea dioxides as reducing agents for disulfides was thought to be applicable to more complex organic compounds bearing disulfide functionality. In particular, it was envisaged that disulfides and aldehydes or ketones can be successfully reduced chemoselectively, in the presence of other functional groups such as nitriles and protected-amines.

For the purposes of identifying new applications of thiourea dioxide, established substrates such as sulfoxide,[84] nitro[87] and azo[87, 88] compounds were not investigated. The higher reactivity of *N,N'*-diisopropylthiourea dioxide and other potential dioxide derivatives could be investigated for these substrates.

Chapter 4. Mechanism of decomposition of disubstituted thiourea dioxides

A survey of the literature concerning the mechanism of the decomposition of thiourea dioxides will quickly reveal how controversial this topic is. It is generally accepted that at high pH, thiourea dioxide is a precursor to a radical anion $SO_2^{\cdot-}$, as determined by EPR studies[75, 78] and from dimerisation[35] to give dithionite ions $S_2O_4^{2-}$. Discussions are now focused on how the $SO_2^{\cdot-}$ radical anion is generated. The following studies carried out were designed in an attempt to contribute to this debate.

Two candidate substrate classes were selected for the purposes of understanding the mechanism, namely *N*-tosylsulfimides and cyclopropylketones.

N-Tosylsulfimides are known to reduce to their corresponding sulfide in moderate to good yields under heterogeneous phase-transfer conditions with thiourea dioxide.[83] As a continuation of published work, it was thought that an improvement in the reduction of sulfimides with novel thiourea dioxides could be realised and also provide a useful protocol to understanding the mechanism of decomposition of thiourea dioxide derivatives.

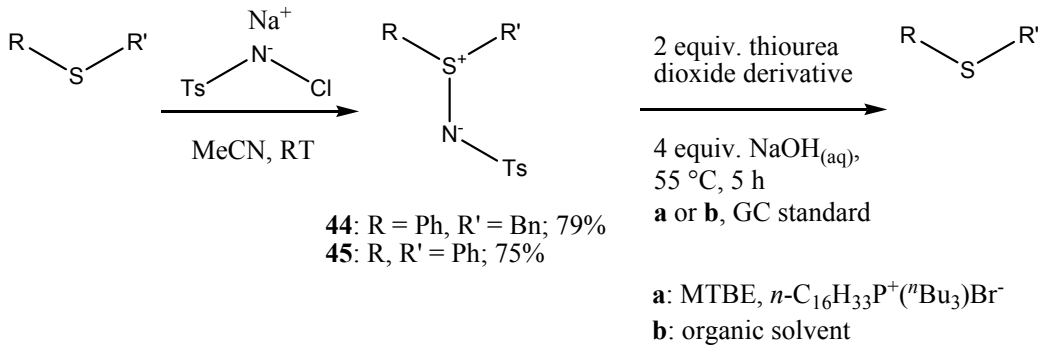
Cyclopropylketones have been successfully utilised as SET probes.[100] This was achieved by determining the relative degree of carbonyl reduction compared to cyclopropane ring-opening. It was therefore desirable to employ cyclopropylketones in order to provide additional evidence for the existence of radical anions.

What follows is a discussion on the preparation of the sulfimides and a study which compares the reducing ability of thiourea dioxides. A mechanistic study is then described which makes use of sulfimide (4.1) and cyclopropylketone substrates (4.2).

4.1 Reduction of sulfimides with disubstituted thiourea dioxides

The reduction of sulfimides has been carried out under heterogeneous phase-transfer and, to a lesser degree, homogeneous conditions.[83] The poor solubility of thiourea dioxide in ethanol or other organic solvents may have been the reason as to why homogeneous conditions were not developed to the same extent as heterogeneous conditions. The inclusion of alkyl functionality on the disubstituted thiourea dioxides isolated (chapter 2) was thought to lead to their higher solubility in non-aqueous media. Therefore, it was of interest to establish if disubstituted thiourea dioxides could give improved reducing properties under simpler homogeneous conditions.

The sulfimides utilised throughout this project were all synthesised *via* the reaction of the sulfide with a nitrene source, chloramine-T trihydrate.[149] The sulfimides were then reduced to the corresponding sulfide with the thiourea dioxide derivative (Table 10). The conversions were determined from GC analysis using 1,3,5-tri-*tert*-butylbenzene as the internal standard.



44: R = Ph, R' = Bn; 79%
45: R, R' = Ph; 75%

Scheme 53. Synthesis and reduction of *N*-tosylsulfimides

The analogues of thiourea dioxide were tested as reducing agents towards sulfimides under biphasic heterogeneous conditions. Under these conditions, it was found that the substituted analogues showed comparable reducing ability to the parent dioxide.

$(RHN)_2CSO_2$		% conversion of sulfimide to sulfide (GC)	
	R	**44** Ph(Bn)S=NTs	**45** Ph_2S=NTs
3	H	67	62
25	*i*-Pr	55	49
26	$-(CH_2)_3-$	54	63
17	Cy	57	62

Table 10. Reduction of sulfimides with thiourea dioxide derivatives

N,N'-Dicyclohexylthiourea dioxide **17** was found to be insoluble in standard aqueous and organic solvents. Propylenethiourea dioxide **26** was found to be the most difficult to isolate. With apparently little difference between the conversions listed in Table 10, it was decided that further mechanistic studies would be carried out using *N,N'*-diisopropylthiourea dioxide **25**. Dioxide **25** was the easiest to prepare and was predicted, from computational and X-ray crystallographic data, to be a more effective reducing agent as evident from the longer C-S bond in **25** compared with thiourea dioxide.

4.1.1 Effect of solvent

It had already been established that *S*-benzyl-*S*-phenyl-*N*-tosylsulfimide **44** could be reduced with thiourea dioxide **3** under homogeneous conditions in ethanol.[83] From our investigations, dioxide **25** was found to reduce sulfimide **44** under monophasic homogeneous conditions in other solvents (Table 11).

	% conversion (GC)	
Solvent	**3** $(NH_2)_2CSO_2$	**25** $(i\text{-}PrNH)_2CSO_2$
ethanol	71	99
THF	66	66
1,4-dioxane	64	66
acetonitrile	12	28
benzene	[a]	8
cyclohexane	[a]	3
DCM	[a]	7
DMF	[a]	>99

a: Not studied

Table 11. Reduction of *S*-benzyl-*S*-phenyl-*N*-tosylsulfimide 44 with dioxides 3 and 25 in different solvents

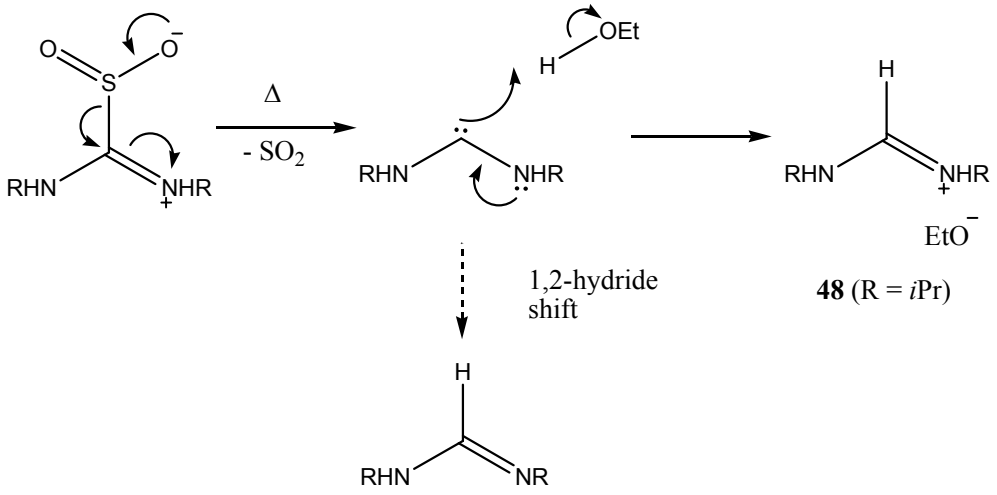
The novel dioxide **25** was found to reduce sulfimide **44** in ethanol to a higher degree than the parent dioxide **3**, under homogeneous conditions. This was thought to result from the improved solubility of dioxide **25** compared with **3** in ethanol. The higher conversion was also attributed to the weaker C-S bond of **25** (1.9045 Å, our work) compared with **3** (1.8592 Å, ref. 49), and hence higher yield of reducing species $SO_2^{\cdot-}$. The higher yield of radical anion $SO_2^{\cdot-}$ from dioxide **25** compared with the parent dioxide **3** is in agreement with synthetic studies.[49] As outlined in the thesis introduction (see 1.3), dianion SO_2^{2-} and radical anion $SO_2^{\cdot-}$ species are postulated to be responsible for tissue damage, in which the sulfur reducing species readily reacts with oxygen to generate harmful superoxide, peroxide and hydroxyl radical species.[34, 35] The higher yield of the sulfur containing reducing species from dioxide **25** and from Repine's *N,N'*-dimethylthiourea dioxide[48] may be a reason why substituted thiourea dioxides are more unstable, and hence more toxic, than thiourea dioxide **3**.

Ethanol was considered easier to handle than DMF and found to be the optimum solvent from the series (Table 11). The reaction of *S*-benzyl-*S*-phenyl-*N*-tosylsulfimide with *N,N'*-diisopropylthiourea dioxide in ethanol was repeated on a preparative scale and gave a mixture of *S*-benzyl-*S*-phenylsulfide and *N,N'*-diisopropylurea. The formation of *N,N'*-diisopropylurea is discussed in 4.1.2. *S*-Benzyl-*S*-phenylsulfide **46** was isolated in 80% yield demonstrating that the reduction of *N*-tosylsulfimides can be carried out on a preparative scale at yields corresponding to the GC conversions.

4.1.2 Effect of base

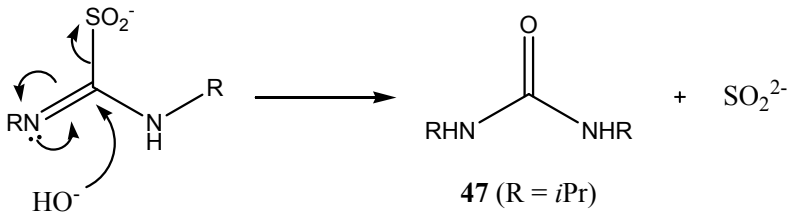
When sodium hydroxide was omitted in the reduction of *S*-benzyl-*S*-phenyl-*N*-tosylsulfimide with *N,N'*-diisopropylthiourea dioxide **25**, no sulfide could be detected by GC. In a separate control experiment, the thermal decomposition of the dioxide **25** in ethanol (without base) resulted in what was thought to be a formamidinium salt. *N,N'*-Diisopropylformamidine (Scheme 54), which could arise from 1,2-hydride shift,[150] was not identified when compared[151] with literature data. The formamidinium salt **48** may have been formed by the elimination of sulfur dioxide followed by rapid protonation of the carbene.[116] This mechanism was also presumed to be applicable to the decomposition of diphenylthiourea dioxide **19** and *trans*-4,5-tetramethyleneimidazolidine-2-sulfinic acid **23**, outlined in chapter 2.

The identity of the counter-anion for **48** could not be verified. The reaction mixture tested negative for dithionite ions.



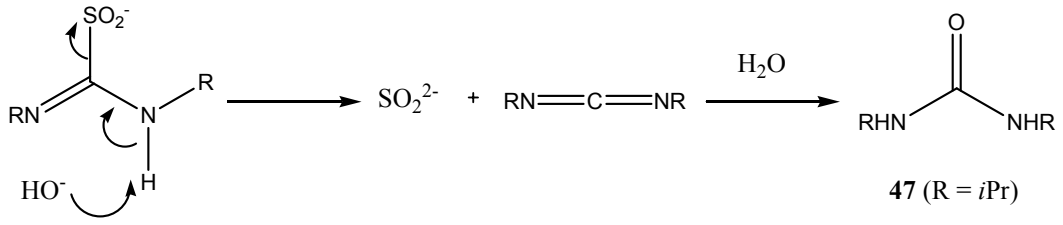
Scheme 54. Decomposition of *N,N'*-diisopropylthiourea dioxide at neutral pH

N,N'-Diisopropylurea **47**, highlighted in 3.1 and 4.1.1, was thought to form as a result of the nucleophilic displacement of the sulfinate group with hydroxide. The formation of the urea **47** was confirmed independently. A 94% yield of the urea **47** was achieved by reacting dioxide **25** with 1.8 equivalents of sodium hydroxide. The urea formed was used as an authentic comparator for all mechanistic studies reported herein. The nature of the sulfur containing leaving group (Scheme 55) is considered in 4.1.3.



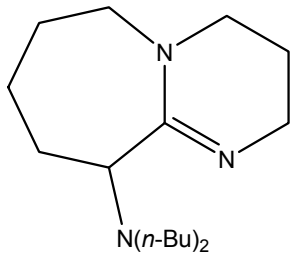
Scheme 55. Heterolytic cleavage of thiourea dioxide *via* nucleophilic addition-elimination mechanism

Clearly, an E2 mechanism could also operate to give the carbodiimide, which rapidly hydrolyses to give the urea **47**.

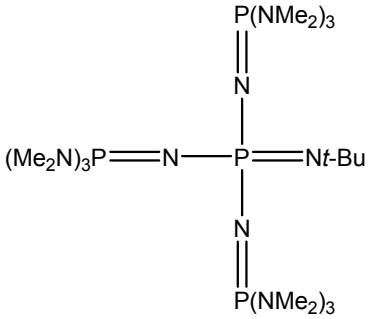


Scheme 56. Heterolytic cleavage of thiourea dioxide *via* a E2 mechanism

A series of organic bases, triethylamine, DBA-DBU, pyridine, DMAP and P_4-phosphazene base, were used in place of sodium hydroxide under the homogeneous conditions set out in Scheme 53 (conditions **b**, in ethanol) to probe the formation of the reducing species *via* a E2 pathway over a nucleophilic addition-elimination pathway.



DBA-DBU
6-(Di-*n*-butylamino)-1,8-diazobicyclo [5.4.0]undec-7-ene



P_4-Base (Fluka)
1-*tert*-Butyl-4,4,4-tris(dimethylamino)-2,2-bis [tris(dimethylamino)-phosphoranylidenamino] -2λ^5,4λ^5-catenadi(phosphazene)

Base	% yield of sulfimide 44 to sulfide 46
Pyridine	0
DMAP	6
Triethylamine	42
DBA-DBU	18
P_4-phosphazene	0

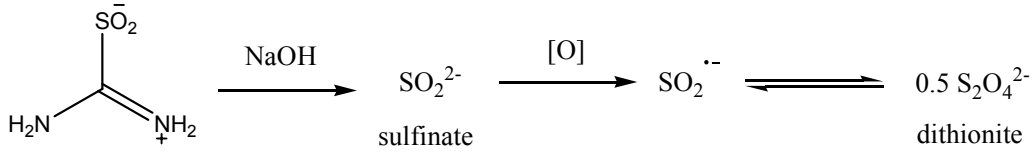
Table 12. Effect of organic bases on decomposition of *N,N'*-diisopropylthiourea dioxide

The organic bases, in Table 12, are listed in order of increasing base strength.[152] The 80% yield of sulfide **46** obtained with sodium hydroxide was not obtained with any of the organic bases listed in Table 12. An E2 mechanism (analogous to Scheme 56) would be favoured by the stronger bases. This is not observed, for example with the very strong P_4-base,[153] and we therefore exclude the elimination mechanism.

These results support the literature observation that dissociation of the C-S bond for *N,N'*-diisopropylthiourea dioxide occurs *via* a nucleophilic addition-elimination reaction, generating the corresponding urea and a sulfur containing species.[34, 35, 49]

4.1.3 Nature of the primary decomposition species

Another issue with regard to the mechanism was the identity of the primary decomposition product of thiourea dioxides with sodium hydroxide. Other authors have proposed that thiourea dioxide in sodium hydroxide affords the sulfinate dianion SO_2^{2-} *via* heterolysis of the C-S bond followed by rapid oxidation to the radical anion $SO_2^{\bullet-}$. The radical anion is known to dimerise and form dithionite $S_2O_4^{2-}$, isolated in their study.[34, 35] The authors found that dithionite formation only occurred under aerobic conditions. Under anaerobic conditions no dithionite was detected. They propose that the radical anion is not the primary species formed from the reaction of thiourea dioxide with sodium hydroxide, but that the sulfinate dianion SO_2^{2-} is the primary product of decomposition.

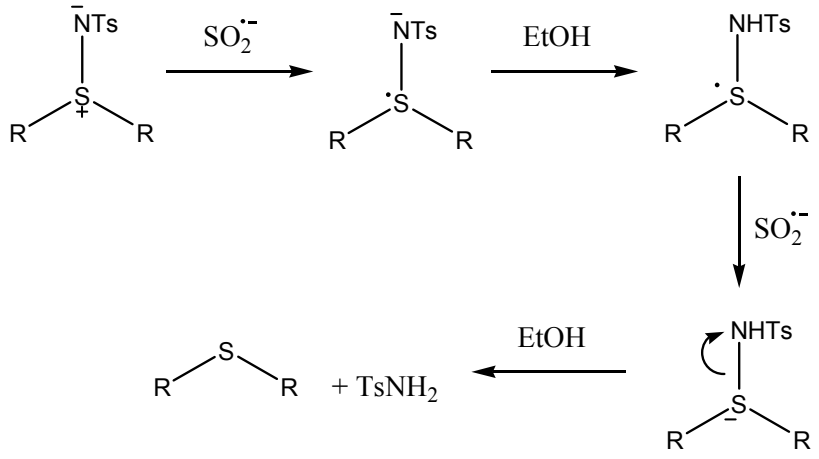


Scheme 57. Formation of sulfur reducing species from thiourea dioxide

An alternative mechanism which potentially generates both dianion and radical anion species *via* homolysis is discussed later in this section (Scheme 63). The following arguments will assume that the heterolysis mechanism in Scheme 55 (see 4.1.2) is in

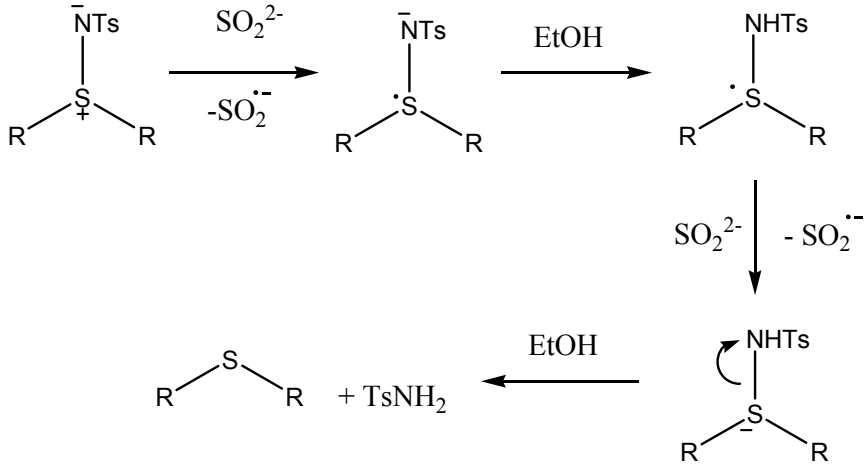
operation and that two reducing species are available. The reduction pathway is considered to proceed through either a SET or a nucleophilic pathway.

a) SET from the radical anion $SO_2^{\bullet-}$. Two electrons are required to lead to S-N bond dissociation. Two equivalents of thiourea dioxide are required to generate two moles of the radical anion, as shown in Scheme 58.



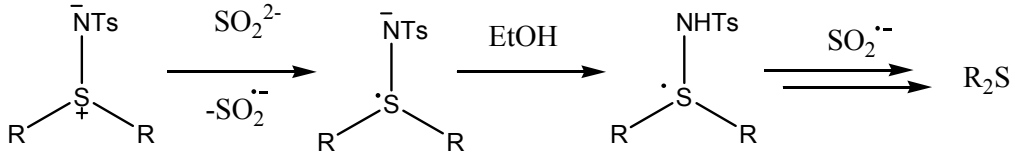
Scheme 58. Radical anion $SO_2^{\bullet-}$ SET reduction

b) SET from the dianion SO_2^{2-}. The radical anion is assumed be unreactive to reducing the sulfimide radical intermediates. This pathway requires two moles of sulfinate dianion *i.e.* two equivalents of thiourea dioxide.



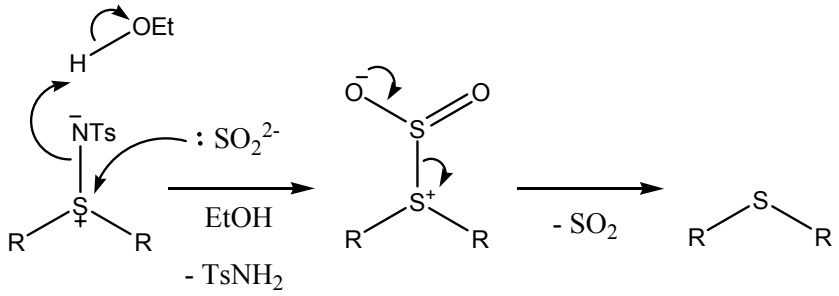
Scheme 59. Dianion SO_2^{2-} SET reduction

c) Successive SET from the dianion and the radical anion. This assumes both species are likely to reduce the sulfimide intermediates. The mechanism is similar to a) and b), but both species provide electrons. Therefore, only one equivalent of thiourea dioxide is required (Scheme 60).



Scheme 60. Successive dianion SO_2^{2-} and radical anion $SO_2^{\bullet-}$ SET pathway

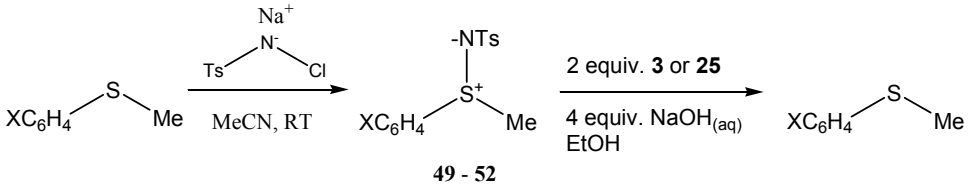
d) Nucleophilic substitution of *N*-tosyl group with dianion. Therefore, only one equivalent of thiourea dioxide is required.



Scheme 61. Dianion SO_2^{2-} nucleophilic substitution-elimination mechanism

Indeed, combinations of the mechanism a) to d) could be envisaged. A series of experiments, using sulfimides **44** and **49-52**, were carried out to help identify the most likely mechanism taking place.

I. **Reduction occurs *via* a SET pathway**. A series of sulfimides **49-52** bearing electron-withdrawing and -donating groups were prepared from the respective sulfide and chloramine-T (% yields listed in Table 13).[149] The sulfimides were then reduced to the corresponding sulfide with thiourea dioxide **3** and *N,N'*-diisopropylthiourea dioxide **25**.



Scheme 62. Synthesis and reduction of *S*-aryl-*S*-methyl-(*N*-tosyl)-sulfimides 49 - 52

		% conversion of sulfimide to sulfide (GC)	
	Sulfide to sulfimide		
X	**% yield**	**3**	**25**
49, H	58	17	37
50, *p*-Me	26	39	43
51, *p*-Cl	69	29	40
52, *p*-Ac	22	53	67

Table 13. Isolation and reduction of *S*-aryl-*S*-methyl-(*N*-tosyl)-sulfimides

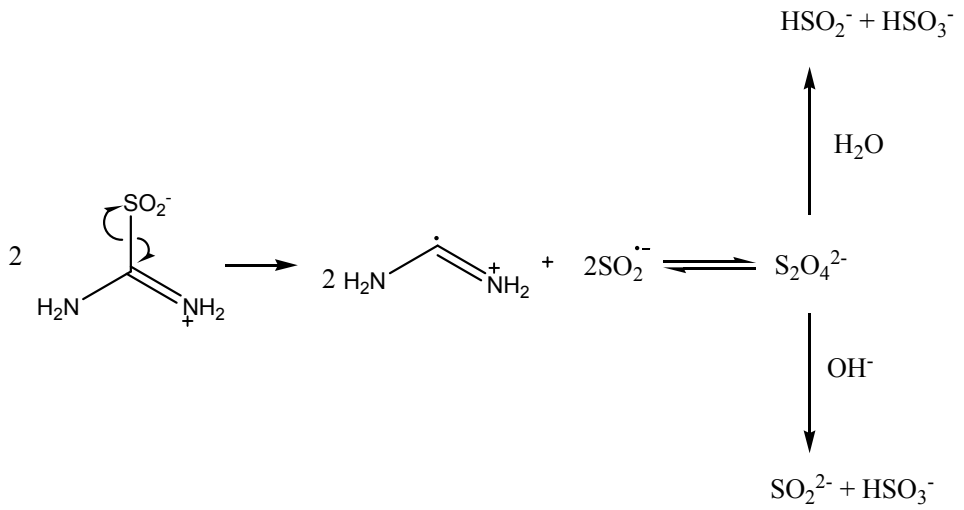
N,N'-Diisopropylthiourea dioxide **25** was found to be a stronger reducing agent than thiourea dioxide **3** for the conversion of *S*-aryl-*S*-methyl-(*N*-tosyl)-sulfimides to the respective sulfides. More importantly, sulfimides bearing both electron-withdrawing or -donating groups were converted to their respective sulfides at higher conversions than the parent sulfimide. This suggests that stabilisation of a radical containing intermediate, as outlined in mechanism a) and/or b), is taking place. This makes mechanism d) unlikely.

II. **Successive SET from the dianion and radical anion is unlikely.** It was found that two equivalents of *N,N'*-diisopropylthiourea dioxide **25** quantitatively reduces the sulfimide **44** to the corresponding sulfide. When 1 equivalent of **25** is used the conversion is halved (44%) *i.e.* 2 moles of dioxide **25** appear to be required to reduce 1 mole of sulfimide **44**. Successive SET from the dianion

followed by the radical anion is described by mechanism c), stating that 1 mole of dioxide **25** should reduce 1 mole of sulfimide **44**. Our observations contradict this proposal. Therefore, mechanism c) seems unlikely.

III. **Primary decomposition species is oxidised to the reducing species.** Both anionic sulfur containing species have been shown to be oxygen-sensitive.[95, 154-156] Therefore two experiments, one under a strict nitrogen atmosphere and one subjected to a continuous air stream, were carried out using two equivalents of reducing agent **25**. Under strict nitrogen conditions the sulfimide (**44**) conversion was lower at 65% than the quantitative conversion obtained under ambient oxygen levels. Aerated conditions inhibited the reduction of the sulfimide entirely. This could therefore show that oxygen is required to oxidise a decomposition species to one which is capable of reducing the sulfimide. The aerated conditions could give rise to oxidation of the dianion and radical anion[35] before either species has a chance to reduce the sulfimide. One explanation is that the sulfinate dianion is oxidised to the radical anion, which is in agreement with published data (Scheme 57).[35] This eliminates mechanisms b) and d), both of which make use of sulfinate dianions. In other words, the existence of a reduced form of the dianion SO_2^{2-} was too difficult to envisage and oxidation from the dianion to the radical anion seems more plausible.

IV. **Decomposition species initiated *via* homolytic C-S bond cleavage is unlikely.** As mentioned earlier in this section, it was postulated that thiourea dioxide generates the radical anion *via* homolytic cleavage of the C-S bond.[65, 75] However from III, molecular oxygen was found to be required for the reduction of the sulfimide. The following scheme involves homolytic cleavage of the C-S bond forming both reducing species, the radical anion $SO_2^{\cdot-}$ and sulfinate dianion SO_2^{2-}, without oxygen. This mechanism is not supported by our data.



Scheme 63. Homolytic cleavage of the C-S bond[65, 75] to generate dithionite $SO_2^{\bullet-}$ and subsequent SO_2^{2-}/HSO_2^- formation[157]

In summary, it appears that the mechanism of reduction operates *via* a SET process provided by the radical anion $SO_2^{\bullet-}$, as outlined in Scheme 58. The findings presented are in agreement with the work of others.[35, 49]

It was now of interest to investigate if the mechanism of reduction would operate similarly for ketones in view of the multiple reports of dissolving-metal reductions.[101, 137, 138, 157]

4.2 Mechanism of reduction of ketones with thiourea dioxide derivatives

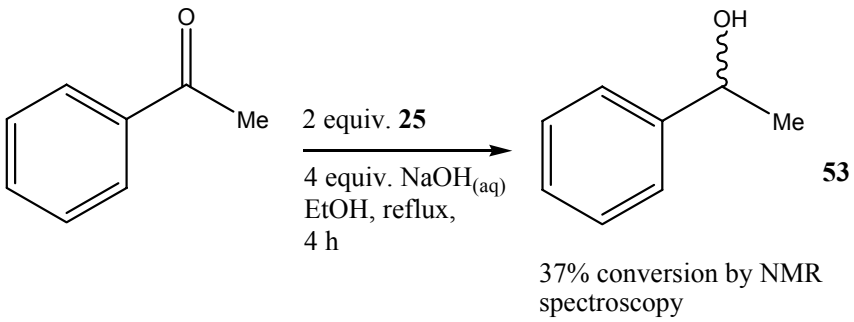
SET probes have been employed to demonstrate mechanistic pathways involving radical intermediates when using samarium diiodide,[158] lithium-ammonia[159] and Grignard reagents.[160] It was of interest to develop the initial investigations concerning the reduction of carbonyl groups (see 3.1) in view of the possibility that SET pathways, as predicted for sulfimides, could take place.

Nakagawa and Minami have found that the reduction of fluorenone with thiourea dioxide in sodium hydroxide takes place *via* a SET process as determined from EPR spectroscopy.[78] Chung reported on the reduction of cyclopropylphenylketone with sodium dithionite but could only isolate the corresponding alcohol with the cyclopropane

ring intact. If SET processes were in operation then it was expected that ring-opened ketones would be isolated.[100] However, the reliability of the SET probe employed by Chung for mechanistic studies was questioned by others. From later reports, it was suggested that ring-opening for some cyclopropylketones (effected by SET reduction), was reversible. [161]

After a thorough analysis of the literature, an aryl-alkyl cyclopropylketone was chosen to meet the needs of our study. Timberlake and Chen published their findings outlining the product distribution of the reduction of 2,2-dimethylcyclopropyl-4-methylphenyl ketone **54** with samarium diiodide, proposing that the mechanism of reduction proceeds *via* a SET process.[158]

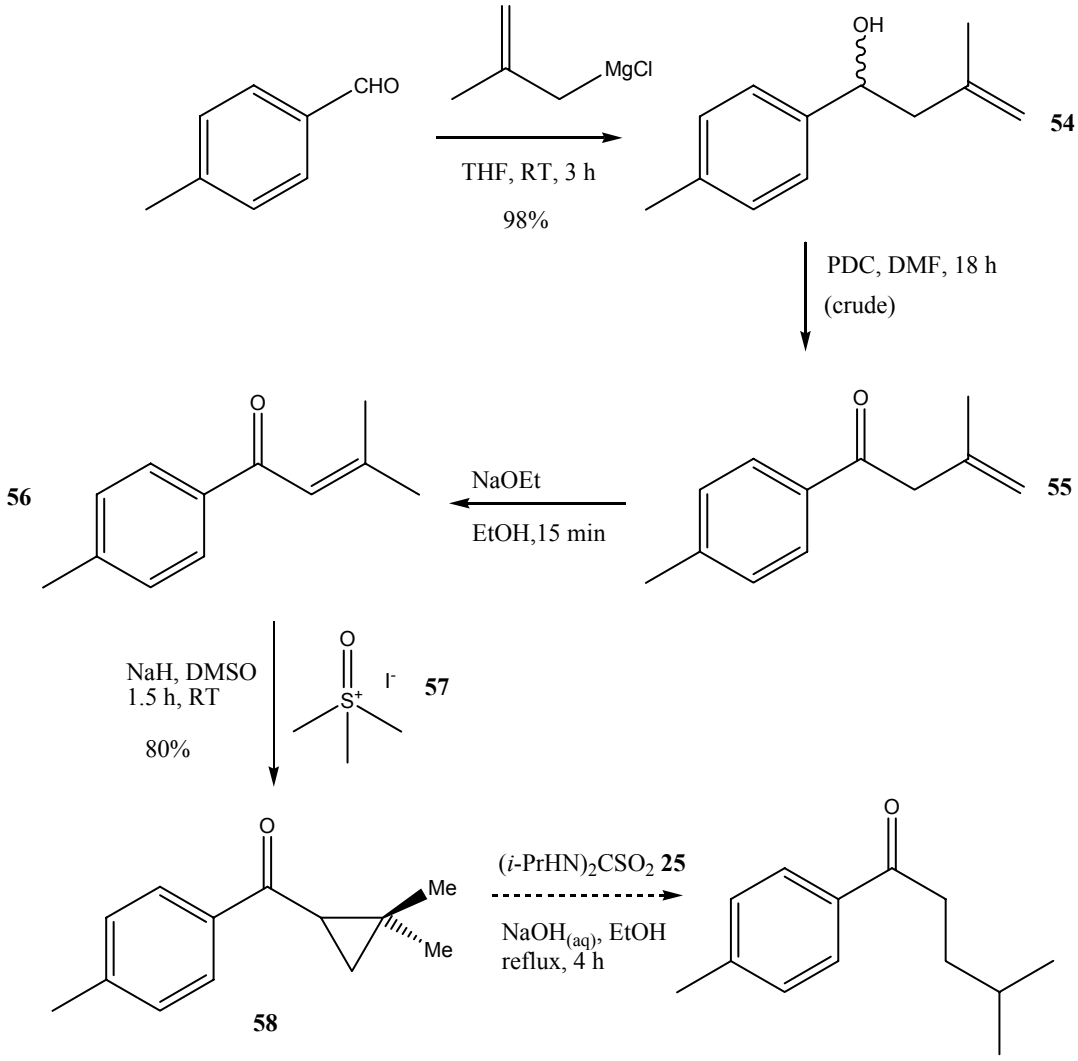
The reduction of an aryl-alkyl ketone with a thiourea dioxide derivative has not been investigated in this project. Given that the synthesis of the SET probe would involve several steps, it was of high priority to identify potential pitfalls associated with this reaction. Acetophenone was tested for this purpose and was reacted with the novel dioxide **25** in ethanolic sodium hydroxide.



Scheme 64. Reduction of acetophenone with *N,N'*-diisopropylthiourea dioxide 25

After successfully reducing acetophenone to phenylethanol **53**, it was decided that the SET probe described by Timberlake and Chen would be employed towards investigating the mechanism of reduction of carbonyl compounds.

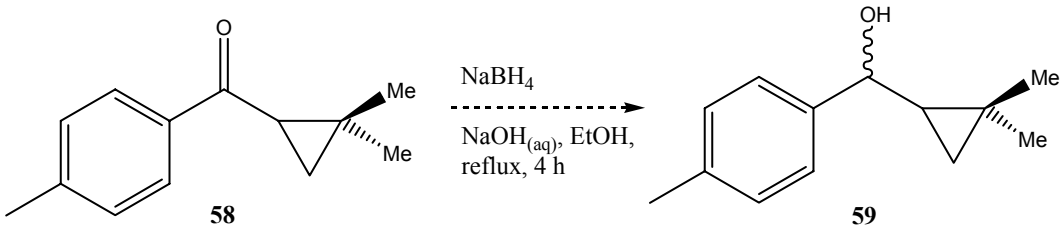
The procedure by Roberts[162] and Corey[163] was followed for the synthesis of the 2,2-dimethylcyclopropyl-4-methylphenyl ketone **58**. Ketone **58** was then reacted with two equivalents of *N,N'*-diisopropylthiourea dioxide **25** in sodium hydroxide (Scheme 65).



Scheme 65. Synthesis and reduction of 2,2-dimethylcyclopropyl-4-methylphenyl ketone 58

Unfortunately, the crude mixture was found to contain the starting ketone and *N,N'*-diisopropylurea **47**, as determined by NMR spectroscopy. The procedure was repeated with higher quantities of reducing agent **25** (10 equiv.) and sodium hydroxide (20 equiv.) but unfortunately resulted in no change.

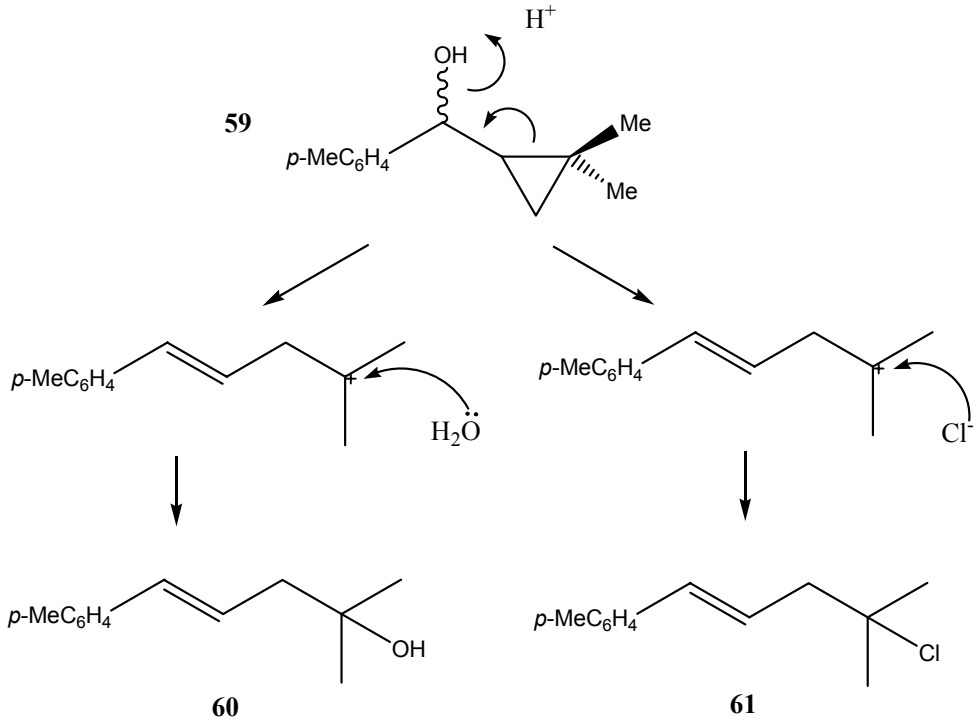
Sodium borohydride was then employed to establish the product distribution of the reduction of **58** and see if chemoselective reduction of the carbonyl group in preference to the cyclopropane ring would take place with hydride reducing agents. Timberlake and Chen did detect the cyclopropyl alcohol by GC and gave conversions from the ketone (Scheme 66).[158] However, they had to synthesise **59** (as an authentic comparator) from other undisclosed methods.



58 **59**

Scheme 66. Borohydride reduction of 2,2-dimethylcyclopropyl-4-methylphenyl ketone

On acidic work-up and chromatographic purification, the cyclopropyl alcohol **59** could not be isolated. Instead ring-opened products **60** and **61** were isolated and thought to arise due to facile dehydration of the cyclopropyl alcohol **59**, as outlined in Scheme 67. Ring opening was favoured because of the stabilisation of the carbocation intermediate.



Scheme 67. Dehydration of 1-(2,2-dimethylcyclopropyl)-1-(*p*-tolyl)methanol 59

In summary, the cyclopropyl ketone **58** was successfully prepared. Reduction with the dioxide **25** failed. The reduction was carried out in parallel with sodium borohydride, in order to isolate the expected cyclopropyl alcohol **59** as an authentic sample. Unfortunately, the alcohol **59** was not isolated. Instead, the products of the HCl work-up were identified, spectroscopically, as *E*-alkenes, **60** and **61**. The identification of the *E*-alkenes was made on the basis of the olefin ^{1}H NMR coupling constants, at 15.6 Hz, which were thought to be too high for *Z*-alkenes.[164] The alkyl halide **61** could only be isolated in low 1% yield and was thought to form *via* nucleophilic attack of the stabilised carbocation with chloride ions from HCl during work-up (Scheme 67). Alcohol **60** was isolated in 43% yield and fully characterised.

Unfortunately, we were not able to use the SET probe **58** to elucidate the mechanism of reduction by dioxide **25** since reduction was too slow. We also note that probe **58** should be used with care. In particular, making deductions based on the absence of alcohol **59**,

which is the expected product of a two-electron reduction, is dangerous since the alcohol itself is prone to ring-opening rearrangements.

4.3 Future Work

The mechanism of the decomposition of substituted thiourea dioxides has been indirectly proven through a series of control experiments. Further refinement to the mechanism could be directed towards identifying pathways, through established spectroscopic techniques including EPR and UV.

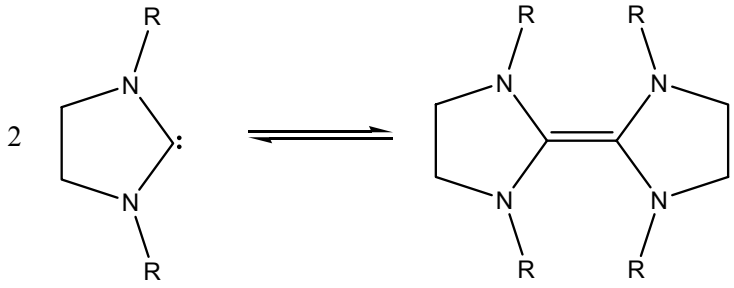
One key area, which may put the debate of decomposition of thiourea dioxides to rest, is the detection of amidine radicals. If the mechanism does proceed *via* homolytic dissociation of the C-S bond in the dioxide, then it may prove beneficial to establish the presence of the amidine radical cation. The authorities of this area have focused almost entirely on the sulfur leaving group but have not focused on the amidine moiety. Perhaps the primary amidine radical cation $(NH_2)_2C^{\cdot+}$ generated from the parent thiourea dioxide is unstable to detection. If this is the case, amidine radical cation analogues, and consequently substituted thiourea dioxides, could be developed so as to demonstrate the validity of the decomposition mechanism presented in the literature so far.

Chapter 5. Investigation into substituted thiourea dioxides as *N*-heterocyclic carbene precursors

For 5-membered *N*-heterocyclic carbenes, referred to as NHCs in the remainder of this work, it is known that unsaturated derivatives are easier to isolate than saturated derivatives. The main reasons are because of the slow rate of dimerisation[165] and relatively higher resistance to hydrolysis.[166]

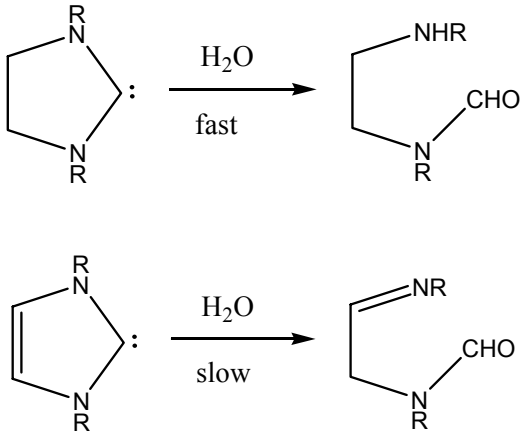
The reason why unsaturated NHCs are more stable to isolate than saturated NHCs is partly due to aromatic stabilisation. Aromatisation of unsaturated NHCs arises from the delocalisation of two olefinic pπ-electrons and two nitrogen lone pairs.[150, 165, 167] The carbenic centre, in the singlet state, is sp^2 hybridised and characterised by an empty p-orbital and a lone pair of sp^2 electrons exo to the heterocycle. Neighbouring electron-donating groups *e.g.* a nitrogen lone pair, stabilise carbene singlet states over triplet states.[168] The lack of olefinic pπ-electrons, and consequently aromatic stabilisation, in saturated NHCs gives rise to relatively more reactive species.

The dimerisation of saturated NHCs is characteristic of their high reactivity. Dimerisation is thought to place through attack from the sp^2 lone pair to the empty p-orbital of a second carbene.[165, 169] The mechanism leads to the formation of a tetraazafulvalene and the generation of a new C=C bond. Calculated bond strengths of the C=C bond of unsaturated tetraazafulvalenes are less than the C=C bond of analogous saturated tetraazafulvalenes.[170] Indeed, it is proposed by some that an equilibrium between dimerisation and dissociation, known as the Wanzlick equilibrium,[171] is significant. This mechanism is still a matter of considerable debate.[172]



Scheme 68. Dimerisation of saturated NHCs to tetraazafulvalenes (tetraaminoethenes)[173]

The rate of hydrolysis of NHCs is also influenced by the degree of aromatisation. It is known that dihydroimidazolin-2-ylidenes rapidly hydrolyse instantly to give ring-opened formamides. This is in contrast to imidazolin-2-ylidenes in which hydrolysis takes months to go to completion.[166]



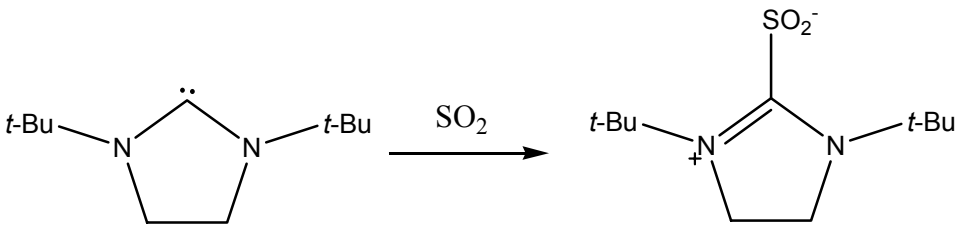
Scheme 69. Hydrolysis[166] of saturated and unsaturated NHCs

It was assumed that both carbenes are also 'air-sensitive'.[173, 174] However, the reactivity was later thought to be due to residual moisture under ambient conditions. Indeed, both carbenes (R = *tert*-Bu, Scheme 69), in the absence of catalysts, are inert to triplet oxygen.[166]

The synthesis of NHCs has been outlined in several reports. The most common methods involve the deprotonation of the formamidinium salt[175] with strong bases[166, 167, 174] or the

reductive desulfurisation of thiourea precursors with potassium metal.[173, 176] The exploration of other routes has received less attention. Most saturated NHCs were isolated with sterically bulky *e.g. N-tert*-butyl[166, 173, 177] or *N*-(2,6-diisopropylphenyl)[178] substituents. It was of interest in this project area to investigate if *N,N'*-dialkylethylenethiourea dioxides could act as precursors to NHCs and offer an alternative synthetic strategy to NHC synthesis.

Interestingly, Denk and co-workers published work which demonstrates that thiourea dioxides could be considered as NHC-sulfur dioxide adducts.[47] They managed to isolate *N,N'*-di-*tert*-butylimidazolidin-2-ylidene sulfur dioxide adduct **9** (alternatively *N,N'*-di-*tert*-butylethylenethiourea dioxide) by the reaction of the respective carbene with sulfur dioxide. However, it remains unreported as to whether adduct **9** could be used as a synthon for carbenes.



9

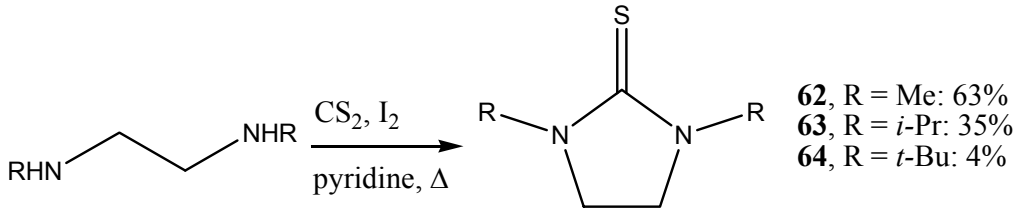
Scheme 70. Synthesis[47] of *N,N'*-di-*tert*-butylethylenethiourea dioxide 9

The potential elimination of sulfur dioxide gas to provide a driving force for the formation of metal carbene complexes was of particular interest. The work reported herein attempts to establish if tetrasubstituted thiourea dioxides could act as carbene precursors.

What follows is an account of the efforts made to synthesise *N,N'*-dialkylethylenethiourea dioxides.

5.1 Preliminary studies concerning the oxidation of *N,N'*-dialkylethylenethiourea

It was envisaged that the oxidation of *N,N'*-dialkylethylenethioureas, in line with work presented in chapter 2, would afford the desired carbene-precursor. A series of thioureas **62**-**64** were synthesised following literature procedures, involving the reaction of the respective diamine with carbon disulfide in the presence of catalytic quantities of iodine.[179]



Scheme 71. Synthesis[179] of *N,N'*-dialkylethylenethiourea

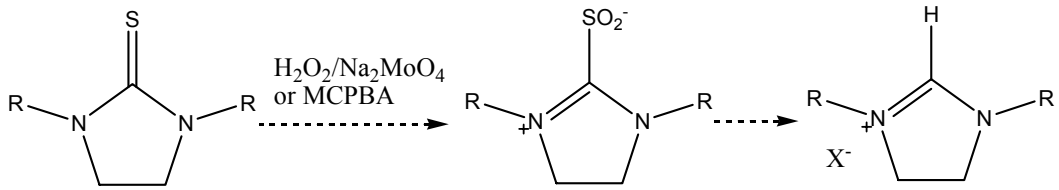
As expected, sterically bulky thioureas such as **64** were more difficult to isolate than the less hindered thiourea **62**.

A brief computational study of the corresponding dioxides **9**, **65** and **66** with DFT B3LYP 6-31G(d,p) in the gas phase was carried out to predict the structures. The calculations revealed that the dioxides would probably be difficult to isolate as demonstrated by the considerably longer C-S bonds *cf.* thiourea dioxides described in 2.3. The weak C-S bond found in **9**, **65** and **66** suggests that the elimination of sulfur dioxide to give the carbene was highly favourable.

Dioxide	**C-S /Å**
3 $(NH_2)_2CSO_2$	2.01849
25 $(i\text{-PrNH})_2CSO_2$	2.04329
31 $(MesNH)_2CSO_2$	2.02106
6 $[HN(CH_2)_2NH]CSO_2$	1.95927
65 $[MeN(CH_2)_2NMe]CSO_2$	2.29569
66 $[^{i}PrN(CH_2)_2N^{i}Pr]CSO_2$	2.30370
9 $[^{t}BuN(CH_2)_2N^{t}Bu]CSO_2$	2.48809

Table 14. Calculated C-S bond lengths predicted with DFT B3LYP 6-31G(d,p)

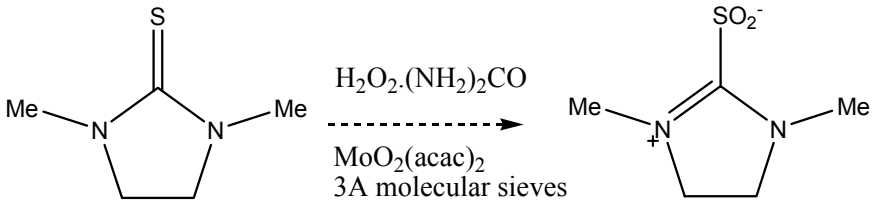
All the ethylenethioureas **62-64** were oxidised with hydrogen peroxide under catalytic conditions similar to that used in 2.1.1, and with 3-chloroperbenzoic acid. Unfortunately, none of the corresponding dioxides could be isolated under these conditions and gave reaction mixtures thought to contain formamidinium salts.



Scheme 72. Oxidation of *N,N'*-dialkylethylenethioureas 62-64

The characteristic $-SO_2^-$ sulfinate stretching modes were not identified by IR spectroscopy which, as discussed previously, was thought to provide a useful non-invasive technique for characterising the dioxides. Dithionite anions, characteristic of the decomposition pathway of thiourea dioxides, were not detected in any of the reaction mixtures. An NMR study revealed non-exchangeable formamidinium CH signals at *ca.* 8 ppm and found to couple with ^{13}C peaks at *ca.* 150 ppm as determined from HMQC NMR experiments.

It was thought that the stability of the dioxides was influenced to a considerable degree by the presence of water. Therefore, it could be envisaged that hydrogen peroxide was an unsuitable oxidising agent in view of the fact that water is generated on oxidation. An attempt at oxidising the methyl thiourea **62,** with hydrogen peroxide-urea adduct in the presence of molecular sieves, gave rise to a mixture of the starting thiourea and formamidinium salt.



62

Scheme 73. Oxidation of *N,N'*-dimethylethylenethiourea with H_2O_2.urea adduct

The analogous oxidation of **62** with hydrogen peroxide in carbon tetrachloride[28] gave only starting material, as observed from TLC and NMR spectroscopic analyses. The oxidation of thiourea **62** with aqueous peracetic acid furnished a mixture, in which only the corresponding formamidinium salt was identified.

Water sensitivity was already observed for ethylenethiourea dioxide **6** as discussed in 2.1.3, and therefore the approach to isolate the dioxides was revised. A series of oxidising agents under non-aqueous conditions were chosen to effect the isolation of the dioxides. *N,N'*-Dimethylethylenethiourea dioxide **65** was predicted to be the most stable disubstituted ethylenethiourea dioxides listed in Table 14 and was chosen as the target for identifying suitable oxidising conditions.

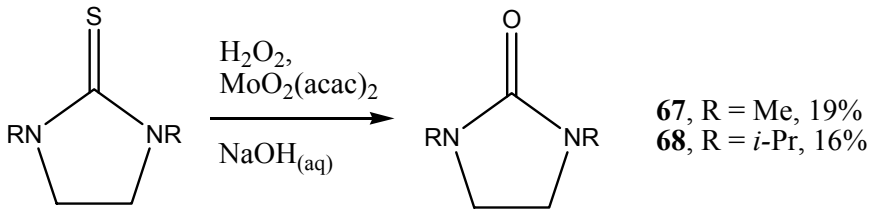
The oxidation conditions investigated are summarised below and found to give a mixture of products.

Oxidising conditions	**Result**
TPAP (cat.), NMO (2 equiv.), DCM	Thiourea and urea (NMR)
NMO (2 equiv.), DCM	Thiourea, unknown mixture (NMR)
$KMnO_4$ (2 equiv.), MnO_2 (5.5 equiv.), DCM[180]	Thiourea and urea (NMR)

Table 15. Oxidants investigated for isolation of *N,N'*-dimethylethylenethiourea dioxide 65

Under the conditions set out in Table 15, it was thought that the dioxide was formed *in situ* but decomposed to the corresponding formamidinium salt or urea.

Full characterisation data on the respective ureas of thioureas **62** and **63** could not be found in the literature although they have been studied. Thus, authentic samples of *N,N'*-dimethylimidazolidin-2-one **67** and *N,N'*-diisopropylimidazolidin-2-one **68** were independently prepared from the respective thiourea with basic hydrogen peroxide. Urea formation was thought to take place *via* the reaction of sodium hydroxide with the respective thiourea dioxide formed *in situ* from the hydrogen peroxide oxidation.



Scheme 74. Preparation of substituted imidazolidin-2-one derivatives

As already mentioned in chapter 2, it was discovered that the isolation of propylenethiourea dioxide **26** proved difficult. On the other hand, *N,N'*-diisopropylthiourea dioxide **25** was isolated, in high yield, from commercially available *N,N'*-diisopropylthiourea. Therefore, **25** was chosen as the target for identification of suitable non-aqueous oxidising conditions for the isolation of the disubstituted ethylenethiourea dioxides.

5.2 Identification of aprotic oxidising agents

Two particular classes of aprotic oxidising agents were considered: dioxiranes and oxaziridines.

5.2.1 Dioxiranes

Derivatives of dioxirane, such as dimethyldioxirane DMDO and methyl(trifluoromethyl)dioxirane TMDO, are powerful oxidising agents and are known to oxidise saturated hydrocarbons to alcohols and aldehydes/ketones[181] and alkenes to epoxides.[182] More importantly, DMDO was shown to selectively oxidise sulfides to sulfoxides[182] and thioketones to sulfines.[183]

Therefore, it was decided the *N,N'*-diisopropylthiourea would be oxidised with DMDO **69** and TMDO **70** to establish the protocol that would be applied to the oxidation of ethylenethioureas. The procedure by Murray was followed and involved the formation of DMDO from dry acetone and Oxone.[184] A gas scrubber, attached at the end of DMDO generator (Figure 20) was filled with saturated aqueous potassium iodide.

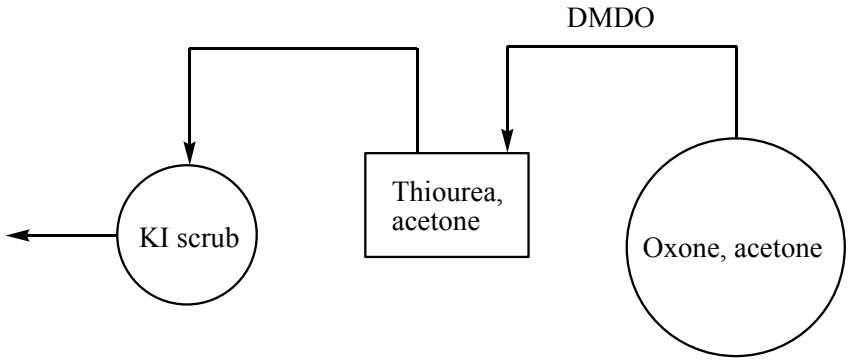
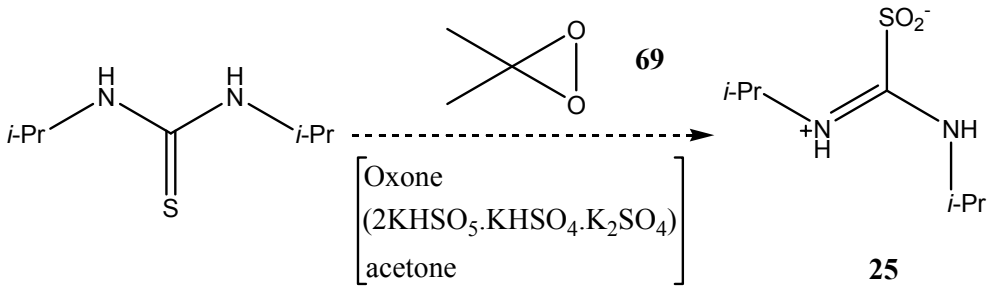


Figure 20. DMDO generator

Fresh colourless solutions of potassium iodide are a standard test for peroxides and change to a yellow solution on oxidation. The scrubber contents were then titrated with 0.001 N sodium thiosulfate to determine the quantity of unreacted oxidising agent, presumably DMDO, that bypassed the reaction.



Scheme 75. Oxidation of *N,N'*-diisopropylthiourea with DMDO

When Murray's procedure was followed, the condensation of a yellow solution of DMDO **69** in acetone was not observed. The isolation of DMDO in acetone was thought to be highly sensitive to the temperature and pressure of the generator. Numerous attempts at following Murray's procedure, where two equivalents of DMDO were bubbled through a solution of the thiourea in dry acetone, were unsuccessful. It is known from our work that *N,N'*-diisopropylthiourea dioxide is insoluble in acetone. However, the precipitation of the dioxide did not occur. Instead, peroxides were detected qualitatively with iodine-starch strips and with sodium iodide/acetone/acetic acid solution in the thiourea solution flask. The thiourea flask was found to contain *N,N'*-diisopropylurea **47** as shown from TLC and NMR spectroscopic analyses. The scrubber had also changed into a yellow solution and, on titration with sodium thiosulfate, was found to have scrubbed two equivalents (to thiourea) of DMDO. Therefore, it was thought that a theoretical quantity of oxidant had bypassed the thiourea solution.

A modified procedure where oxone, acetone and the thiourea were reacted in the same flask *i.e.* DMDO generated *in situ* was also unsuccessful. The reaction mixture was complex (as judged by NMR spectroscopy) and only *N,N'*-diisopropylurea could be identified.

TMDO **70** was found to be more volatile than DMDO. Attempts at repeating the bubbling procedure analogous to the above for DMDO led to a complex mixture where only the starting material was identified (as judged by NMR spectroscopy). Titration of

the scrubber with sodium thiosulfate revealed that 2½ equivalents of TMDO to thiourea had bypassed. When the *in situ* method was applied to TMDO, only *N,N'*-diisopropylurea could be identified from the complex mixture as shown by NMR spectroscopy.

Overall, DMDO was thought to have oxidised the thiourea to the dioxide but probably reacted further to lead to urea formation. The *in situ* procedure did not yield any improvement. TMDO was too volatile and thought to have bypassed the thiourea solution when bubbled through. In addition, TMDO was found to have oxidised the thiourea when used *in situ* but may also reacted with the dioxide.

In light of the practical difficulties and safety implications of DMDO and TMDO employed, it was decided that no further development of the dioxirane protocol would be carried out. Work was therefore directed towards alternative oxidising agents: oxaziridines.

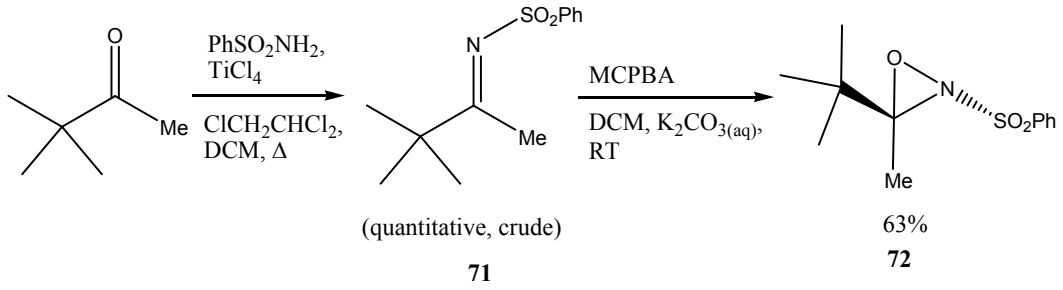
5.2.2 Oxaziridines

The application of oxaziridines has been reviewed by Davis[185] and Sheppard.[186] The authors highlighted that substituents on the oxaziridine ring influence the relative degree of nitrogen-transfer[187] and oxygen-transfer reactions. In particular, *N*-sulfonyloxaziridine chemistry was featured predominantly in oxidation reactions, for example, in the controlled oxidation of organosulfur compounds.

Perrio and co-workers have shown that *N*-sulfonyloxaziridines can be used in the oxidation of thiols to sulfoxides.[188] They made use of *trans*-3-(1,1-dimethylethyl)-3-methyl-2-(phenylsulfonyl)oxaziridine **72** and was therefore chosen as an oxidising agent for our research.

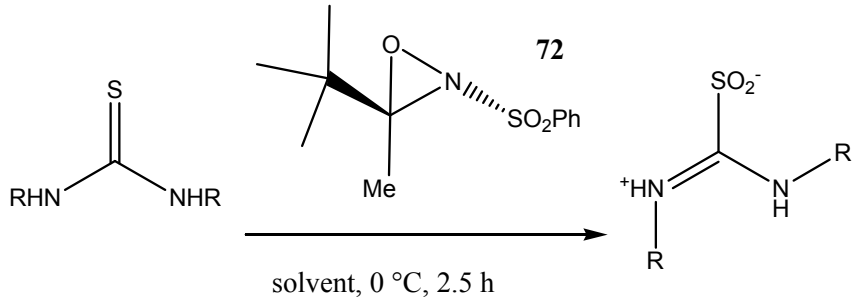
The oxaziridine **72** was synthesised following Perrio's two-step procedure[189] and found to be stable for at least two months under a blanket of nitrogen, at room temperature in the

dark. However, it was discovered that oxaziridine **72** reacts with d_6-dimethylsulfoxide, probably through oxidation, because the NMR spectrum of **72** was initially found to compose of a mixture. After six hours at room temperature, the NMR spectrum would compose entirely of the respective imine **71**.



Scheme 76. Synthesis[189] of oxaziridine 72

N,N'-Diisopropylthiourea was successfully oxidised to the respective dioxide **25** in 83% yield (Table 16, entry 6). Imine **71** was also recovered crude and used for the preparation of more oxaziridine. In light of this success, it was decided that oxaziridine **72** (two equivalents to thiourea, unless otherwise stated) should be tested for the isolation of the other thiourea dioxide derivatives discussed in this project. The results were encouraging and are summarised in Table 16.



Scheme 77. Oxidation of substituted thioureas with oxaziridine 72

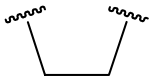
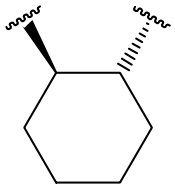
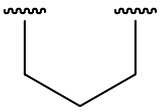
	R	Solvent	Observations
1		CCl_4	Five equivalents **72** gives mixture: trace dioxide **6** and 2-imidazoline **7** with excess of starting thiourea.
2	Cy	3:2 diethyl ether/1,4-dioxane	Dioxide **17** isolated, 96%
3	*t*-Bu	3:2 diethyl ether/1,4-dioxane	Formamidinium salt, as deduced by NMR spectroscopy, crude 38%.
4	Ph	THF or 3:2 diethyl ether/1,4-dioxane	Dioxide not detected *in situ*, unknown mixture by NMR spectroscopy.
5		CCl_4	Dioxide detected *in situ*, NMR spectrum too complex. ^{13}C NMR spectrum similar to spectrum obtained from H_2O_2/CCl_4 conditions
6	*i*-Pr	THF	Dioxide **25** isolated, 83%
7		THF	Dioxide **26** isolated, 81%
8	Mes	3:2 diethyl ether/1,4-dioxane	Dioxide **31** isolated, 80%

Table 16. Oxidation of disubstituted thioureas with oxaziridine 72

It was apparent that the syntheses of ethylenethiourea dioxide analogues (entries 1 and 5), were problematic. The oxidation of ethylenethiourea with oxaziridine **72** was sluggish even in the presence of five equivalents of **72** and only yielded a trace quantity of the dioxide. Interestingly, ethylenethiourea trioxide could not be detected when oxaziridine was used as the oxidant, in contrast to when hydrogen peroxide was used (see 2.1.3). The bicyclic thiourea dioxide **23** could not be isolated with oxaziridine and did not yield any improvement over hydrogen peroxide/carbon tetrachloride conditions (see 2.1.3). The oxidation of propylenethiourea (entry 7) was substantially improved over hydrogen

peroxide conditions as noted by 81% yield of the dioxide **26** with oxaziridine **72** *cf.* 7% yield with hydrogen peroxide (2.3.2). Additionally, when two equivalents of oxaziridine to propylenethiourea were used, no propylenethiourea trioxide **28**, anticipated from over-oxidation or perhaps disproportionation[129, 130] of propylenethiourea dioxide, was observed.

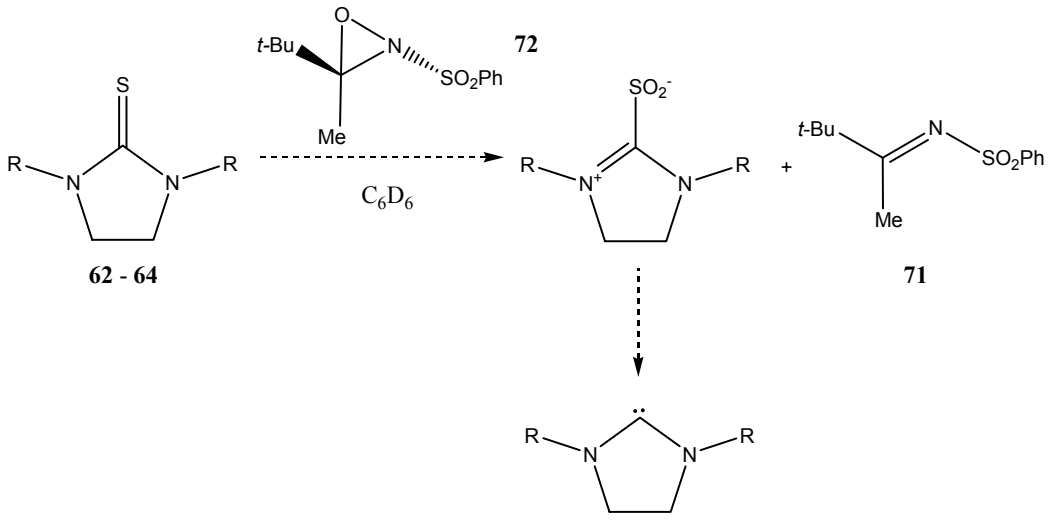
The isolation of *N,N'*-di-*tert*-butylthiourea dioxide **18** (entry 3) could not be achieved with the oxaziridine. It therefore seems likely from our work and from Walter's work,[53] that dioxide **18** is too unstable to isolate. The other acyclic dioxides **17** and **31** (entries 2 and 8, respectively) were successfully isolated in high yield.

The promising results obtained with oxaziridine **72** were then applied to the oxidation of ethylenethioureas **62**-**64**.

5.3 Oxaziridine-mediated oxidation of ethylenethioureas

5.3.1 *trans*-3-(1,1-Dimethylethyl)-3-methyl-2-(phenylsulfonyl)oxaziridine

In view of the potential low stability of NHCs (Scheme 69, chapter introduction) it was decided that the oxidation of ethylenethioureas **62**-**64** should be monitored by NMR spectroscopy. The NMR spectroscopic data of the respective carbenes have been reported by Denk in d_6-benzene.[173]



Scheme 78. Synthesis and decomposition of ethylenethiourea dioxide derivatives

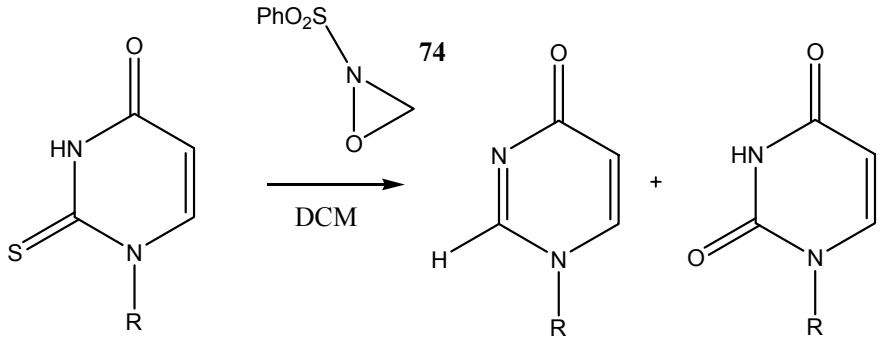
The thiourea was first analysed by ^{1}H NMR spectroscopy to establish adequate concentration and identification in d_6-benzene. The oxaziridine was then added to the NMR sample and sonicated at room temperature for 45 minutes. Proton NMR experiments were then run to monitor the progress of the reaction.

Only the methyl thiourea **62** reacted with oxaziridine **72** as evident from the consumption of thiourea. Unfortunately, the NMR spectrum was complex and contained starting thiourea. The corresponding carbene (R = Me, Scheme 78) could not be identified. The reaction was repeated at higher temperature of 40 ºC but resulted in no change. Both the isopropyl **63** and *tert*-butyl **64** thioureas were unreactive to the oxaziridine and their respective spectra contained starting material. Imine **71**, indicative of oxidant consumption, was detected in all NMR spectra after 45 minutes. In light of these results, the reaction conditions were not developed further. It was thought that the reactions were sluggish on steric grounds and therefore it was decided that smaller oxaziridines would be investigated.

5.3.2 Synthesis of *N*-sulfonyloxaziridines

While there are plenty of examples[186, 188-196] of *N*-sulfonyl-3-substituted oxaziridines reported in the literature, the utility of monosubstituted *N*-sulfonyloxaziridines has

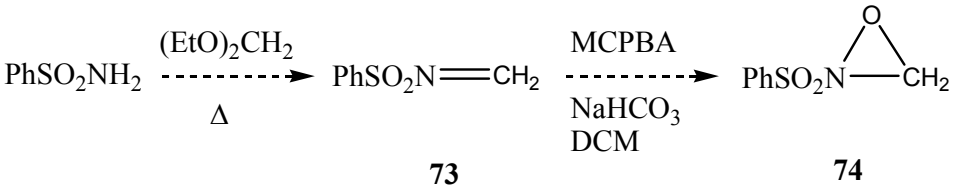
received less attention. For example, the use of *N*-phenylsulfonyloxaziridine PSO **74** employed in the oxidative desulfurisation of 2-thiouridine was the only reported example of monosubstituted oxaziridines.[196]



R = nucleoside

Scheme 79. Oxidation of 2-thiouridine with *N*-phenylsulfonyloxaziridine[196]

The authors did not provide a procedure towards the synthesis of PSO. They indirectly reference other procedures first established by Davis.[191] The synthesis of PSO was therefore presumed to have been carried out as outlined in Scheme 80.



Scheme 80. Synthesis of *N*-phenylsulfonyloxaziridine PSO

The synthesis of PSO was carried out according to Scheme 80 but proved unsuccessful. Only starting sulfonamide could be detected in the product mixture.

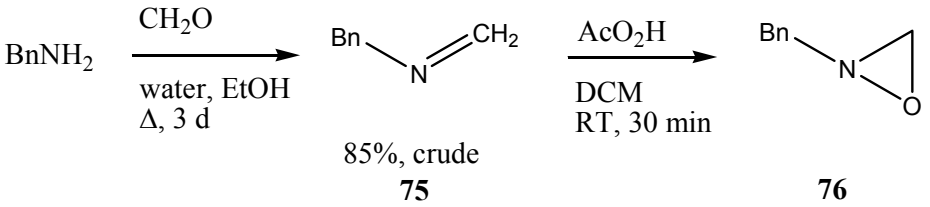
The procedure described in Scheme 80 was modified. Peracetic acid was added to the sulfonamide and acetal mixture. The intention was to deprotect the acetal and oxidise the ensuing imine with peracetic acid. However, only starting sulfonamide was recovered in the product mixture.

Priority towards isolating sulfonyloxaziridines, similar to PSO, was dropped and our focus was directed towards other oxaziridines.

Examples of suitable *N*-substituted oxaziridines, fully characterised, were not found in the literature. Much of the literature solely based on the chemistry of low molecular weight oxaziridines is quite old. In 1957, Emmons had reported that *N-tert*-alkyloxaziridines were isolable and also that *N*-benzyloxaziridine readily decomposed.[197] Two oxaziridines were then chosen based on Emmons' work: *N*-isopropyloxaziridine and *N*-benzyloxaziridine.

5.3.3 Synthesis of *N*-benzyloxaziridine

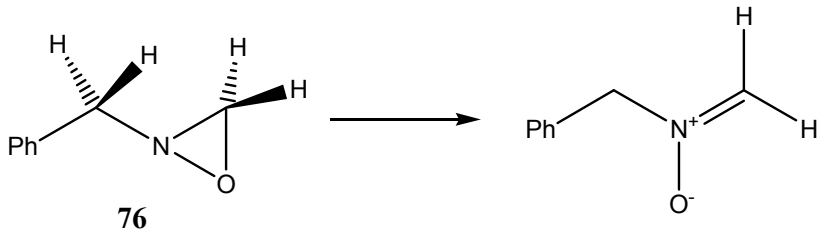
The synthesis of *N*-methylenebenzylamine **75**, reported by Gogoll and co-workers, was followed.[198] The imine was not purified. The oxaziridine **76** was prepared by reacting peracetic acid with imine **75**.



Scheme 81. Synthesis of *N*-benzyloxaziridine 76

Inversion at the nitrogen centre of the oxaziridine ring did not appear to take place at room temperature, as established from NMR spectroscopy. Two sets of diastereotopic CH_2 signals, in d_6-benzene, were observed. Both sets had large coupling constants thought to be due to geminal coupling and characteristic of the benzyl (J = 13.5 Hz) and oxaziridine (J = 10.3 Hz) methylene protons. The assignments were made, based on two factors.[164] The higher H-Ĉ-H angle of the oxaziridine CH_2 results in a smaller J value *cf.* benzyl CH_2 signals. The effect of neighbouring π-bonding for the benzyl CH_2 protons results in a higher J value *cf.* the oxaziridine CH_2 signals. Overall, the J value of

oxaziridine CH_2 < benzyl CH_2. It is known that oxaziridines can rearrange, especially with heat, to nitrones.[186]



76

Scheme 82. Rearrangement[186] of oxaziridines to nitrones

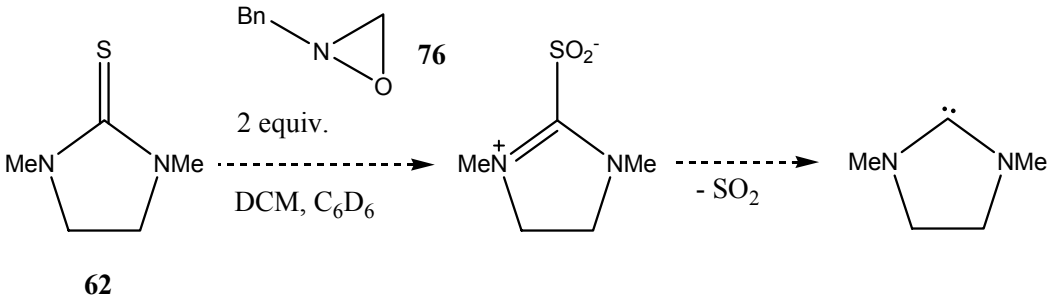
However, the NMR spectroscopic data in d_6-benzene gave rise to two sets of diastereotopic CH_2 signals. If only one set was located in the NMR spectrum, then the oxaziridine CH_2 could be mistaken for terminal olefin signals of the nitrone. The NMR spectroscopic analysis revealed that the oxaziridine structure is probably more likely than the rearranged nitrone. In contrast, NMR spectroscopic data obtained in d_1-chloroform revealed only one set of diastereotopic methylene signals.

Oxaziridine **76** was very unstable and decomposed within minutes if heated above 35 °C or if handled neat. Residual impurities, identified in the imine NMR spectra, were carried across to the oxaziridine NMR spectra. Attempts to distil the crude oxaziridine at reduced pressure also led to breakdown. Dichloromethane solutions of the oxaziridine tested positive for peroxides with sodium iodide/acetic acid/acetone and were found to breakdown after *ca.* 3 days at room temperature (as determined from ^{1}H NMR spectroscopy). In view of the low stability, the conversion of imine **75** to oxaziridine **76** was assumed to be quantitative and the oxaziridine used crude.

5.3.4 *N*-Benzyloxaziridine as an oxidising agent

Two equivalents of *N*-benzyloxaziridine **75** were reacted with the methyl thiourea **62** and initially looked promising from NMR experiments. It appeared that the carbene had formed because both the ^{1}H and ^{13}C CH_3 and CH_2 NMR spectroscopic data of the crude product were in agreement with literature data.[173] However a subsequent HMQC NMR

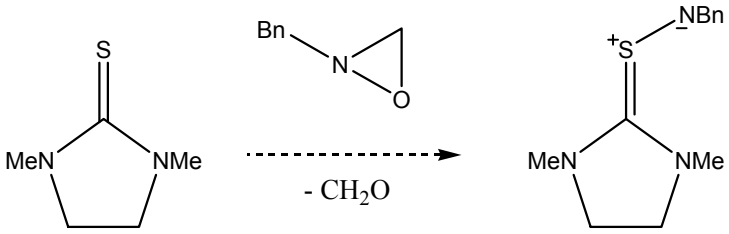
experiment revealed incorrect ^{1}H-^{13}C couplings and proved that the carbene had not been formed as first thought. The identities of the mixture of products remain unknown.



62

Scheme 83. Oxidation of *N,N'*-dimethylethylenethiourea 62 with *N*-benzyloxaziridine 76

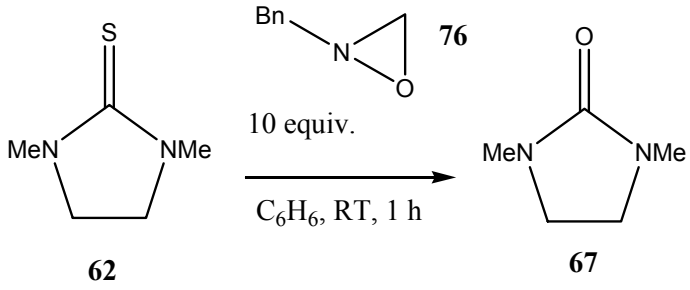
N-Methylenebenzylamine **75**, anticipated as a by-product from the consumption of *N*-benzyloxaziridine, could not be detected in any of the experiments. As mentioned previously, oxaziridines are utilised in nitrogen-transfer reactions.[186, 187] It was thought that the reaction of *N*-benzyloxaziridine with *N,N'*-dimethylethylenethiourea could have resulted in the formation of an *S*-(*N*-benzyl) sulfimide (Scheme 84). This reaction would be accompanied by the formation of formaldehyde.



Scheme 84. *N*-Transfer reactions with oxaziridines

It was discovered that paraformaldehyde was insoluble in the NMR reaction mixture. Additionally, no effort was made to introduce formaldehyde into the mixture. Therefore, the reaction in Scheme 84 could not be verified.

The reaction (Scheme 83) was repeated with five and ten equivalents of oxaziridine **76** but gave mixtures which could not be identified from NMR spectroscopic or GCMS analysis. The NMR study of the reaction of the methyl thiourea **62** with ten equivalents of oxaziridine **76** gave a ^{1}H NMR spectrum which appeared to show two major peaks. This was thought to represent one compound, characterised by one set of methyl and methylene environments. The corresponding urea, *N,N'*-dimethylimidazolidin-2-one **67** was not identified in the spectrum. It was therefore of interest to investigate the identity of the unknown species by repeating the experiment on a preparative level. Several work-up procedures were carried out in order to isolate the unknown compound. Unfortunately, it appeared that the unknown compound decomposed to the urea **67** during the work-up stage.



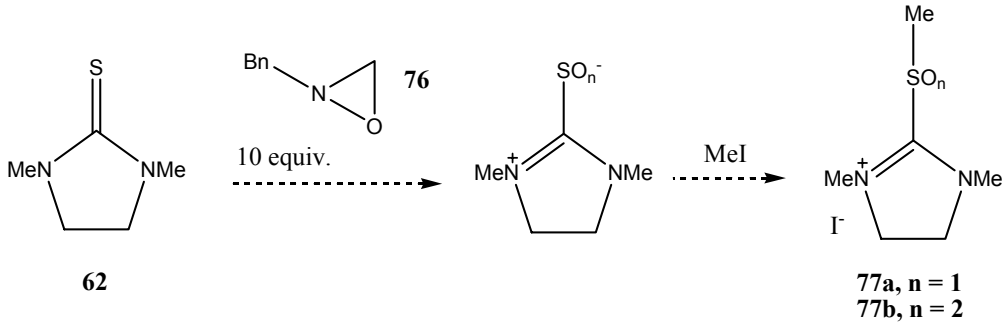
62 **67**

Scheme 85. Reaction of thiourea 62 with oxaziridine 76

The work-up of the crude mixture was carried out with methyl *tert*-butyl ether, 2 M aqueous HCl and saturated Na_2CO_3 solution. The NMR spectra of the extracts were complex and each work-up attempt lead to the formation of *N,N'*-dimethylimidazolidin-2-one **67**.

Analogous NMR studies (Scheme 83) of two and ten equivalents of *N*-benzyloxaziridine **76** to isopropyl **63** and *tert*-butyl **64** thioureas, respectively, gave complex mixtures. Only starting thiourea and residual oxaziridine were detected. The poor reactivity of thioureas **63** and **64** with oxaziridine **76** may have been due to steric hindrance and was not pursued further.

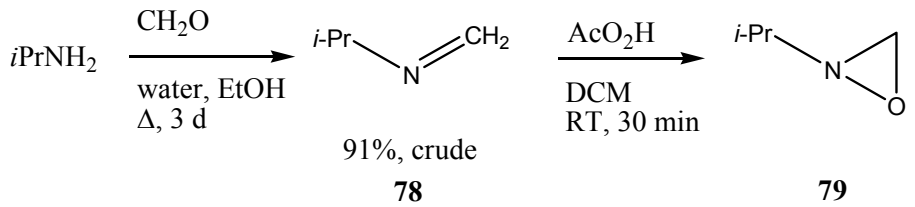
Evidence to suggest that *O*-transfer from oxaziridine **76** to *N,N'*-dimethylethylenethiourea **62**, was lacking. All attempts so far gave the corresponding urea **67** and were not indicative of monoxide or dioxide formation. An attempt to trap an oxide of thiourea **62** with methyl iodide, forming either the corresponding sulfoxide **77a** (n = 1, Scheme 86) or sulfone **77b** (n = 2) and thus indicate that *O*-transfer was taking place (compare with Scheme 84), was investigated. Unfortunately, a complex mixture of compounds was produced, as determined by NMR spectroscopy. Only *N,N'*-dimethylimidazolidin-2-one **67** could be identified in the complex mixture.



Scheme 86. Trapping of oxides of *N,N'*-dimethylethylenethiourea 62 with methyl iodide

5.3.4 Synthesis and application of *N*-isopropyloxaziridine

N-Isopropyloxaziridine **79** was synthesised analogously to the procedures followed for *N*-benzyloxaziridine.



Scheme 87. Synthesis of *N*-isopropyloxaziridine 79

The oxaziridine **79** was handled as a crude solution in DCM. It tested positive for peroxides with sodium iodide/acetic acid/acetone. Inversion at the nitrogen centre was

apparently slow at room temperature, as judged by the diastereotopic CH_2 and CH_3 signals in the NMR spectra. This was thought to be in agreement with the oxaziridine structure (Scheme 87) as opposed to the nitrone structure, discussed previously (Scheme 82, 5.3.3).

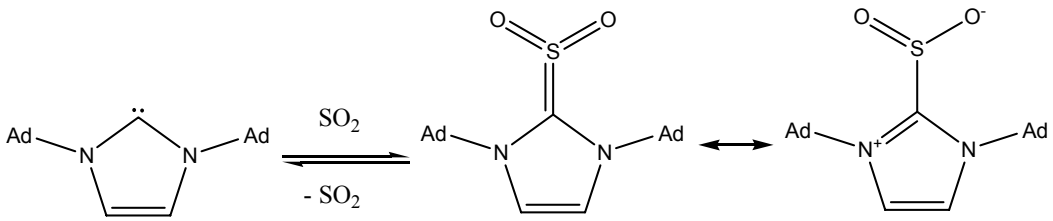
N-Isopropyloxaziridine **79** in DCM was mixed with the methyl **62** and isopropyl **63** thioureas in NMR tubes, and sonicated at room temperature for 30 minutes. The methyl thiourea **62** led to a mixture of unidentifiable products after 30 minutes and became more complex after 3 hours. The isopropyl thiourea **63** was apparently inert to the oxaziridine as demonstrated by the presence of the thiourea and oxaziridine starting materials. Heating both analogues to 40 ºC for 6 hours made no difference to the NMR spectra.

In conclusion to the oxaziridine work presented here, it is apparent that the preparation of NHCs from the reaction of oxaziridines **72**, **76** and **79** with the ethylenethioureas **62** - **64** was unsuccessful. *N,N'*-Dimethylethylenethiourea was the most reactive of the thioureas investigated but generally reacted with the oxaziridines to give unknown mixtures. Oxidation of the bulkier isopropyl and *tert*-butyl analogues was too challenging, probably for steric reasons.

The synthesis of $NHC.SO_2$ adducts has provided a significant challenge! Although ultimately we were not able to prepare these compounds by oxidation of thioureas as hoped, our attempts have led to some interesting new oxaziridine chemistry and improved methods for oxidation of other classes of thioureas. We still hoped to explore whether $NHC.SO_2$ adducts would be useful carbene precursors and therefore proceeded to attempt preparation of model compounds from the corresponding carbenes *via* the literature route.

5.4 Preparation of substituted ethylenethiourea dioxide from carbenes

The structure and isolation of NHC.SO_2 adducts has been debated by several groups. The isolation of a crystalline diaminosulfene (Scheme 88) was reported by Skrypnik and Lyashchuk.[55]



Scheme 88. Carbene-sulfur dioxide adducts by Skrypnik and Lyashchuk[55]

However, the observations were disqualified by Denk and co-workers, who proposed that the compound would more likely possess a pyramidal geometry at the sulfur atom, as demonstrated from computational predictions.[47]

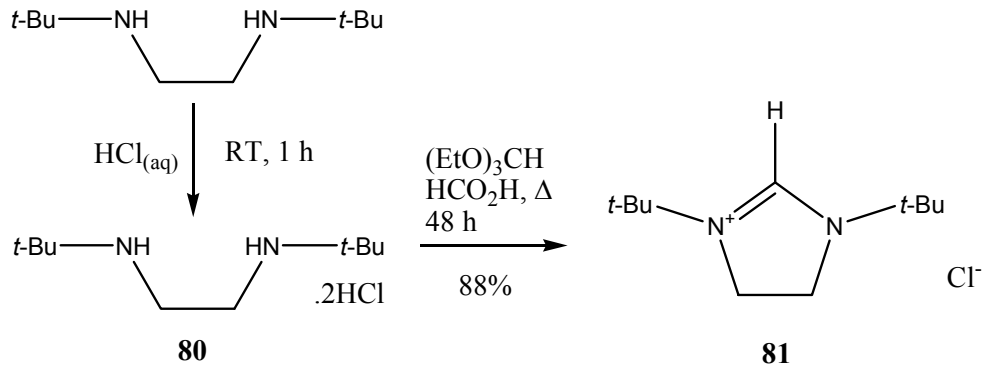
Denk and co-workers managed to isolate a new compound **9** by passing a stream of sulfur dioxide over the NHC in dry THF and described **9** as a Lewis acid-base adduct (Scheme 70).[47]

From our investigations, the synthesis of ethylenethiourea dioxides from the oxidation of the respective thiourea has so far been unsuccessful. Therefore, a means to answer the question as to whether thiourea dioxides can act as NHC precursors was approached by preparing the dioxides *via* Denk's procedures.

5.4.1 *N,N'*-Di-*tert*-butylethylenethiourea dioxide

As mentioned before, NHCs are usually prepared either *via* the deprotonation of the formamidinium salt or the reductive desulfurisation of the thiourea with potassium metal. In light of the difficulty encountered in this work to isolating *N,N'*-di-*tert*-butylethylenethiourea in high yield, it was decided that the carbene would be prepared using the deprotonation protocol.

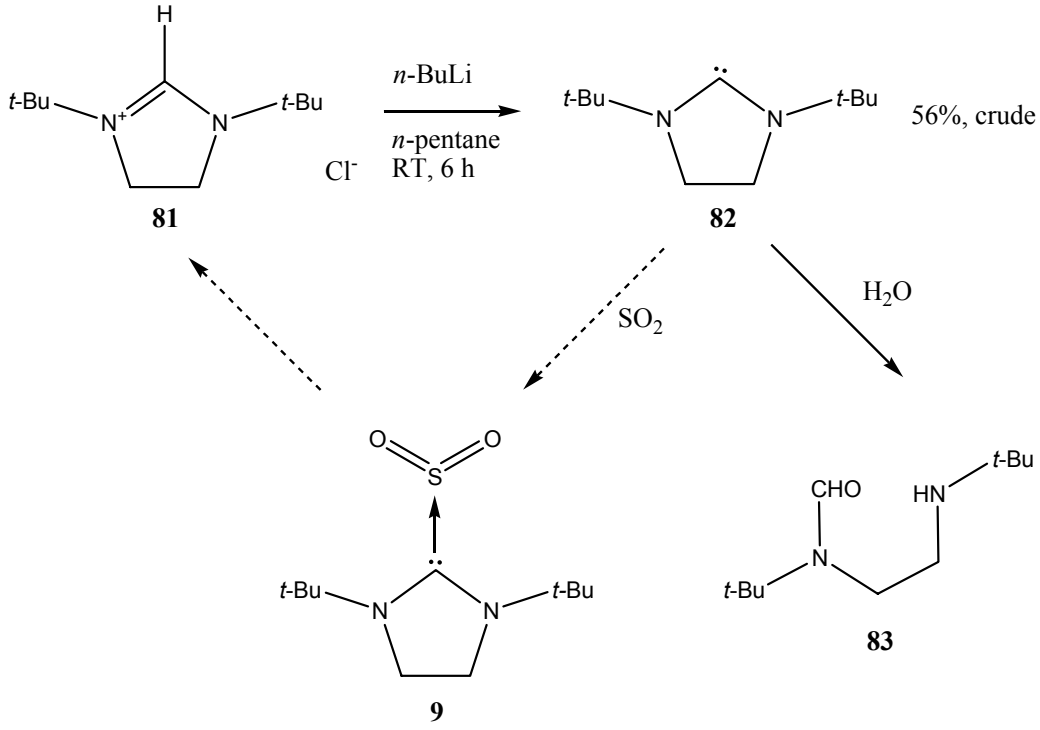
The imidazolinium salt **81** was prepared from literature procedures.[177]



Scheme 89. Synthesis[177] of *N,N'*-di-*tert*-butylimidazolinium chloride 81

Attempts to deprotonate the salt **81** with sodium hydride, frequently gave mixtures of the carbene **82** and a ring-opened formamide **83** (Scheme 90). More consistent success for carbene isolation was achieved using *n*-butyllithium instead of sodium hydride.[166]

The following observations were made using NMR spectroscopy. Carbene **82** was characterised by the ^{13}C carbenic centre at 237 ppm. When handled neat, the carbene was found to remain unchanged under a nitrogen atmosphere for at least a few hours. However, carbene **82** was very sensitive to water as shown by the detection of ring-opened formamide **83** in the NMR spectrum.[166] The carbene in d_6-benzene remained unchanged after standing at room temperature for two days.



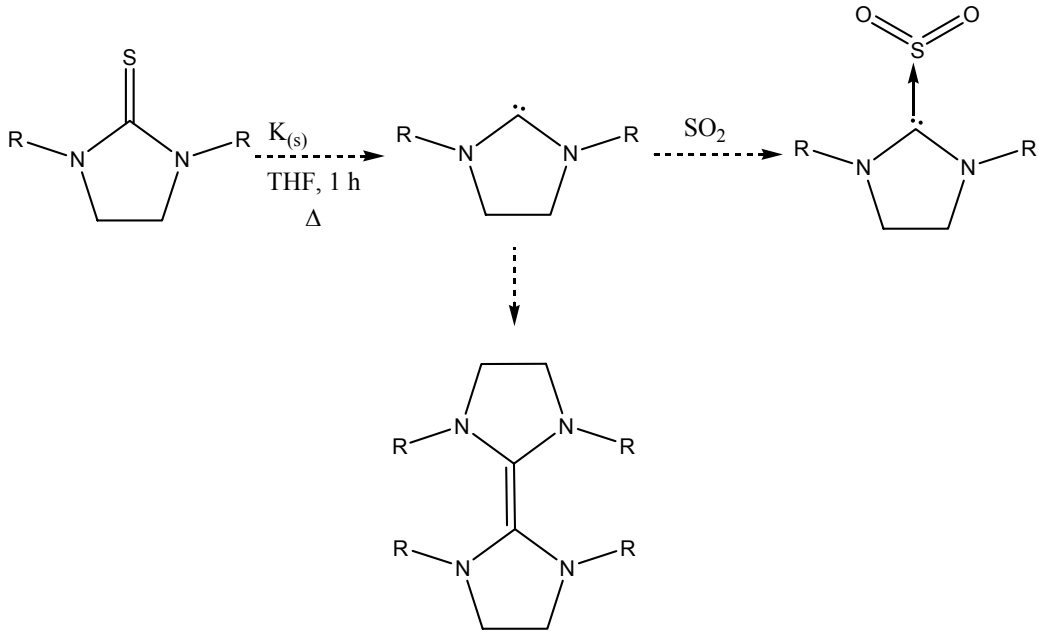
Scheme 90. Synthesis and reactivity of *N,N'*-di-*tert*-butylimidazolin-2-ylidene 82

Carbene **82** was then reacted with sulfur dioxide in accordance with Denk's procedure.[47] Unfortunately, repeated attempts at isolating the sulfur dioxide adduct **9** were unsuccessful and gave buff solids which were insoluble in d_6-benzene. The compound was soluble in d_1-chloroform but gave a compound which corresponded to the salt **81** (counter-anion unknown). According to Denk, the adduct **9** hydrolyses to a formamidinium salt, in which the counter anion was bisulfite HSO_3^-. From our investigations, neither the NHC.SO_2 adduct **9** nor the bisulfite salt could be identified from the NMR spectra of the crude product mixtures.

As mentioned in 5.1, DFT B3LYP calculations predicted that the *tert*-butyl dioxide **9** was very unstable as shown by the long C-S bond length 2.49 Å. The methyl **65** and isopropyl **66** dioxides were also predicted unstable to isolation but to a lesser degree than **9** (C-S bond length < 2.30 Å). Therefore, it was decided that the above adduct formation would be applied to the smaller analogues **65** and **66**.

5.4.2 New adducts *via* Denk's methodology

N,N'-Dimethylethylenethiourea **62** (see Scheme 71, 5.1, R = Me) was readily prepared in good yield. Therefore, it was decided that the respective carbene **84** (Scheme 91, R = Me) would be synthesised *via* the reductive desulfurisation of the thiourea with potassium metal.[173]



Scheme 91. Synthesis and reactivity of *N,N'*-dialkylimidazolin-2-ylidenes

Unfortunately, *N,N'*-dimethylimidazolin-2-ylidene **84** could not be isolated, even for brief periods as a solution. The isolation difficulties were attributed to the rate to which dimerisation[173] to the corresponding tetraazafulvalene **85** took place, as shown from NMR spectroscopic studies. Subsequent addition of sulfur dioxide gas yielded a mixture of compounds. Neither the starting thiourea, *N,N'*-dimethylimidazolidin-2-one, carbene or dimer (R = Me, Scheme 91) were identified in the mixture from NMR experiments. There were apparent broad IR spectroscopic signals corresponding to the sulfinate or sulfonate group. The compound tested negative for dithionite ions and LSIMS did not reveal the presence of parent ions or potassium adducts.

When the isopropyl thiourea **63** was refluxed with potassium, *N,N'*-di-isopropylimidazolin-2-ylidene **86** (Scheme 91, R = *i*-Pr) was successfully prepared. Carbene **86** was easier to handle than the methyl carbene **84** as observed from the slower rate of dimerisation that took place. The carbenic ^{13}C was found at 234 ppm, in agreement with published data[173] and the NMR sample remained unchanged for a few hours before dimerisation took place.

Isolation of the isopropyl NHC.SO_2 adduct **66** was inconclusive. The reaction between carbene **86** and sulfur dioxide gave a product which was only sparingly soluble in d_6-benzene and was therefore analysed in d_1-chloroform. Most of the solvent, THF, was evaporated to give a light gum. NMR spectroscopic analysis revealed the presence of one isopropyl-containing product along with residual THF. Neither the starting thiourea, *N,N'*-diisopropylimidazolidin-2-one **68** nor the respective formamidinium salt were detected in the ^{1}H and ^{13}C NMR spectra. The IR spectrum did not reveal characteristic sulfinate peaks and the compound tested negative for dithionite ions. However, LSIMS did reveal the presence of potassium adducts *i.e.* $[dioxide + K]^+$ and $[dioxide + K_2]^+$ ions and were detected in high abundance (> 90%). The same sample was concentrated further to remove more THF. NMR spectroscopic analysis had now revealed a change in composition, demonstrated by apparent formamidinium salt-type signals, similar to the mixture obtained for the oxidation of thiourea **63** with hydrogen peroxide (see 5.1). From this result, it was thought that the dioxide may have been stabilised in residual THF but decomposed when handled neat. The unknown compound was thought to be *N,N'*-diisopropylethylenethiourea dioxide **66** which decomposed *via* elimination of sulfur dioxide and protonation, (*cf.* Scheme 54, 4.1.2) to yield the imidazolinium salt.

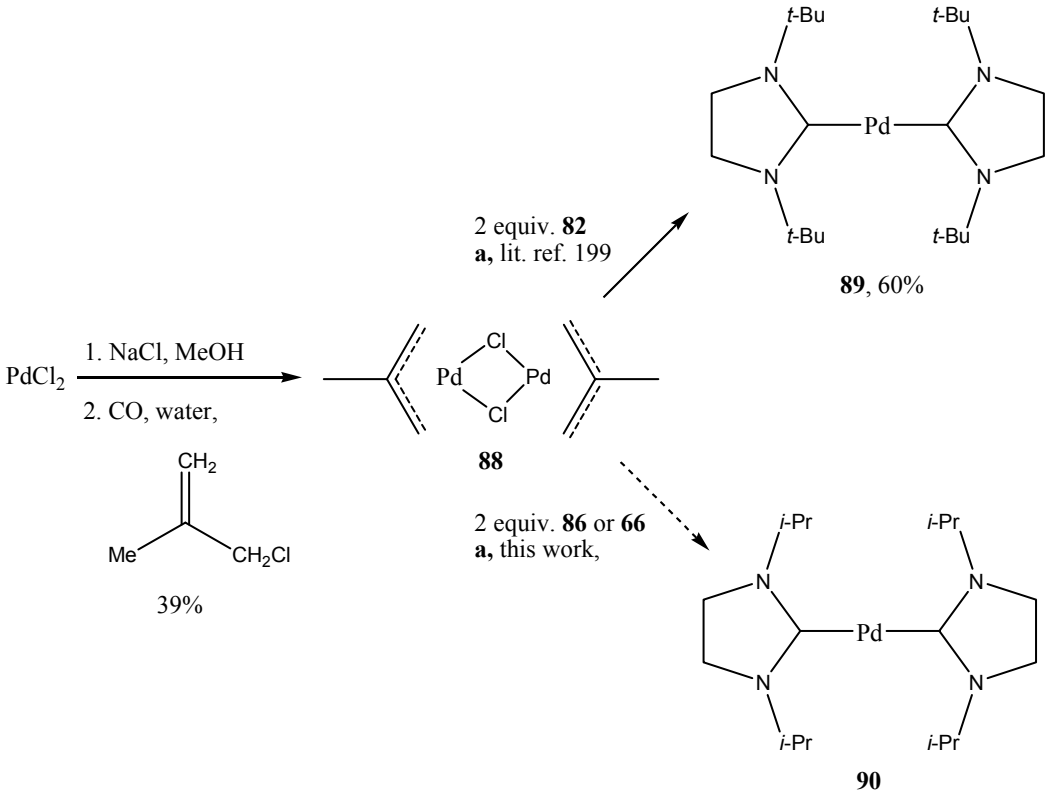
In summary, it appears that the procedure reported by Denk is more difficult than first thought. The literature *tert*-butyl carbene **82** was successfully prepared, however, the subsequent adduct could not be isolated. The methyl **84** and isopropyl **86** carbenes were

more difficult to handle, with the former dimerising within a few minutes and the latter within a few hours. Both compounds gave unknown products when reacted with sulfur dioxide.

The reaction of the isopropyl carbene **86** with sulfur dioxide was thought to give only one unknown product. Therefore, it was decided to repeat the synthesis of, presumably, *N,N'*-diisopropylethylenethiourea dioxide and then immediately use it for the formation of a palladium complex.

5.5 Investigation into the preparation of Pd(0)carbene complexes

Two-coordinate palladium(0) carbene complexes have been utilised by Caddick and Cloke in amination and Suzuki-Miyaura reactions of aryl chlorides.[177] They synthesised the palladium(0) complex **89** (Scheme 92) from bis(methallyl)dichlorodipalladium(II) **88** and the *tert*-butyl carbene **82**. Caddick and Cloke's route[177] was consequently applied, for our purposes, to investigate the synthetic utility of the unknown isopropyl compound **66**.



a: sodium dimethylmalonate, THF, reflux, 18 h (see literature procedure[199])

Scheme 92. Synthesis of imidazolin-2-ylidene palladium(0) complexes

Bis(methallyl)dichlorodipalladium(II) **88** was synthesised from literature procedures.[200] Two experiments were then carried out (Scheme 92).[199] Palladium(II) complex **88** was reacted with a fresh solution of the isopropyl carbene **86** to determine if the novel palladium(0) complex **89** was isolable. For comparison, palladium(II) complex **88** was also reacted with what was thought to be the isopropyl NHC.SO_2 adduct **66** and therefore establish if adduct **66** was a carbene precursor.

When the fresh isopropyl carbene **86** solution was reacted according to Scheme 92 following procedures from the literature, a dark-brown oil was formed. It was evident that the starting carbene was consumed, as demonstrated by the NMR spectrum, however the product was very complex and probably polymeric in composition. Unfortunately,

the same result was obtained when the unknown adduct **66** was used in place of the carbene solution.

To conclude this chapter, it was discovered that *N,N*'-disubstituted ethylenethiourea dioxides are difficult to isolate. Oxidation of the thioureas with hydrogen peroxide, MCPBA or inorganic oxidants *e.g.* permanganate or TPAP did not yield the dioxides. It remains unknown as to whether the dioxides were isolable, given that our brief computational study predicted that the compounds may be too unstable to isolate or detect. However, the seemingly most unstable analogue has been published and fully characterised.[47] As a result, the synthesis of the dioxides (or adducts) was carried out from the carbene with a view to identifying if the dioxides were indeed carbene precursors.

N,N'-Di-*tert*-butylimidazolin-2-ylidene **82** and the isopropyl NHC **86** were successfully prepared following literature procedures.[166] Unfortunately, when **82** was reacted with sulfur dioxide gas, it gave an NMR spectrum which was indicative of the corresponding imidazolinium salt. This may have formed immediately on reaction with sulfur dioxide or on NMR sample preparation.

The reaction between the isopropyl carbene **86** and sulfur dioxide gave an unknown compound which on concentration appeared to decompose to the corresponding imidazolinium salt. The unstable intermediate formed was thought to be a potential candidate as a novel NHC precursor. Overall, the formation of the NHC sulfur dioxide adducts appears to be more complicated than first thought.

5.6 Future Work

The initial studies carried out on the utility of dioxides as carbene precursors have furnished some encouraging results. The detection of *N,N'*-diisopropylethylenethiourea dioxide from mass spectrometry and the detection of one *N*-isopropyl containing

compound from NMR spectroscopic data, could warrant further investigation. This is especially significant when it appeared that the unknown compound decomposed to an imidazolinium salt. Due to time constraints at this stage of the project, the synthesis and characterisation of the dioxide was not repeated. The optimisation of other variables, for example reaction solvent and temperature, could also be revisited so as to isolate the target dioxide.

The application of thiourea trioxides as carbene precursors could also be explored. It may be argued that the higher stability of thiourea trioxides *cf.* thiourea dioxides[1, 28] would render the trioxides unsuitable as carbene precursors. However this has yet to be confirmed. The new studies could lead to the utilisation of trioxides analogues as carbene precursors, an approach which may not be viable from the dioxides.

5.7 Overall conclusions

The key findings are summarised as follows.

1. Molybdate catalysed hydrogen peroxide oxidation of thiourea derivatives successfully yielded a series of symmetrical, *N,N'*-dialkyl and -diarylthiourea dioxides. The stability of the dioxide was thought to be related to the C-S bond length of the dioxide in addition to intra- and inter-molecular hydrogen bonding. Isolation of the compounds was heavily reliant on the low solubility of the dioxides in the reaction solvent.

2. *N,N'*-Diisopropylthiourea dioxide **25** was found to have comparable if not higher reducing ability as compared with thiourea dioxide. This was clearly demonstrated with the reduction of disulfides and sulfimides under simple, mild reaction conditions. The encouraging results have set a strong foundation for further study with regard to the reducing power of other thiourea dioxide derivatives and for the reduction of other disulfide containing compounds. The

improved reducing ability of **25** was attributed to the higher solubility in organic solvents compared with thiourea dioxide **3** and the longer C-S bond length than **3**, deduced from computational and X-ray crystallographic studies.

3. The mechanism of reduction is pH dependent and probably proceeds *via* heterolysis of the C-S bond to furnish the reducing species.

4. The sulfonyl oxaziridine **72** proved to be a useful oxidising agent for the preparation of substituted thiourea dioxides, under non-aqueous conditions. In particular, the dioxides were obtained at comparable if not higher yields with the oxaziridine conditions, compared with aqueous hydrogen peroxide conditions. Over-oxidation of the dioxide to the trioxide was not observed when two equivalents of oxaziridine to thiourea were used. Oxidation of the derivatives of ethylenethiourea, with oxaziridine **72,** was found to be more challenging than the acyclic thioureas investigated.

5. The application of *N,N'*-disubstituted ethylenethiourea dioxides as carbene precursors has yet to be established. However, initial efforts were promising and revealed that the intermediates decompose readily, probably through elimination of sulfur dioxide. The observations outlined here provide solid evidence to suggest that thiourea dioxides are potential NHC carbene precursors

Experimental

Starting materials and solvents were obtained from commercial sources and used as supplied. 1,4-Dioxane and diethyl ether were degassed and bubbled with nitrogen prior to the reaction. Thin-layer chromatography was carried out on commercial aluminium sheets with silica gel (Merck $60F_{254}$). All solvent evaporation procedures were carried out at 35 ºC/16 mbar unless otherwise stated. All manipulations were carried out in air unless otherwise stated.

All NMR spectra were obtained using a Bruker DPX300 (300 MHz) or DPX400 (400MHz) spectrometer with TMS, acetonitrile or 1,4-dioxane used as an internal reference. Coupling constants J are reported in units of Hertz (Hz). MS (EI, CI and LSIMS) was performed by the University of Warwick Mass Spectrometry Service. MS (ESI) was performed using a Bruker Esquire2000 Electrospray Spectrometer. IR spectra were obtained using a Perkin-Elmer Spectrum One FT-IR spectrometer fitted with a Horizontal Attenuated Total Reflectance (HATR) accessory. Elemental analyses were performed by Warwick Analytical Services and by Medac. Melting points were performed on a Stuart Scientific Melting Point SMP10 apparatus and are uncorrected.

All literature compounds and procedures are referenced. Thiourea oxides **25**, **26**, **27**, **28** and **31** isolated, are new compounds. Full characterisation data of known ureas **67** and **68** are unreported in the literature. Compounds **23**, **60**, **61**, **65**, **66**, **76**, **77a**, **77b**, **78**, **79** and **90** are unknown. ^{13}C NMR spectroscopic assignments are grouped. For example, '10.1, 45.7, 159.5 ($3xC_q$), 170.2 (CH)' means that each signal, at 10.1, 45.7 and 159.5 ppm, represents one quaternary carbon centre and the signal at 170.2 ppm represents one methine centre.

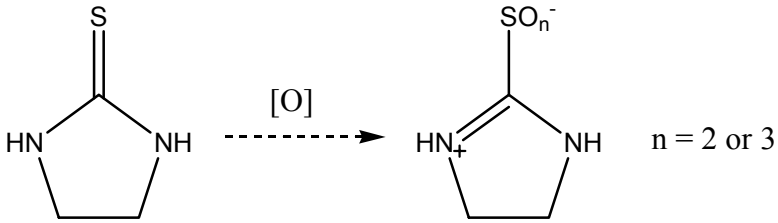
Ammoniacal solutions of naphthol yellow S (0.02% w/w naphthol yellow S in 3 M ammonium hydroxide) were used as a chemical test for the presence of dithionite ions

which are detected by a yellow to pink colour change.[96] On further standing a colourless solution is formed.

Gas chromatography was performed on a Shimadzu GC-17A installed with a BPS5 column (30 m x 0.32 mm; 0.5 μm film thickness) and recorded on a personal computer using Shimadzu ClassVP 4.3 software. The injector was set to 200 ºC and the detector was set to 340 ºC. Helium was used as the carrier gas and set to 1 ml min^{-1} flow rate. Unless otherwise stated, a GC programme of 200 – 300 ºC gradient at a rate of 10 ºC min^{-1} then held at 300 ºC for 6 minutes (total 16 minutes) was utilised for the separation.

Chapter 2 experimental

Ethylenethiourea dioxide 6



Oxidation of ethylenethiourea to give ethylenethiourea dioxide **6** (n = 2) was carried out using different conditions (a)–(c). Each experiment gave different product distributions of the dioxide and the trioxide (n = 3), as deduced by ^{1}H NMR spectroscopy.

a) Catalytic conditions

Following a literature procedure,[1] a three-necked flask was charged with ethylenethiourea (102 mg, 1 mmol), bis(acetylacetonato)dioxomolybdenum(VI) (3 mg, 1 mol%), 1,4-dioxane (5 ml) and diethyl ether (7 ml) and cooled to -5 ºC. 30% hydrogen peroxide (0.23 ml, 2 equiv.) was added and the mixture stirred under a nitrogen atmosphere for 1½ h. The reaction mixture was filtered under a nitrogen atmosphere and washed with ice-cold diethyl ether to furnish an off-white solid which was found to contain a mixture of compounds. A sample tested positive for dithionite ions. The target ethylenethiourea dioxide could not be isolated. ν_{max}(neat)/cm^{-1} 1590 and 1533 (C=N) 1061, 1027 and 1006 (SO_3 or SO_2 stretching); ^{1}H NMR spectroscopic data were consistent with literature data;[66] all peaks are listed. δ_H(300 MHz; D_2O; 1,4-dioxane) 3.58 (<0.1H, s, imidazolidin-2-one CH_2), 3.93 (1H, s, 2-imidazoline CH_2), 4.00 (3H, s, dioxide CH_2), 4.08 (1.4H, s, trioxide CH_2) 8.15 (0.2H, s, 2-imidazoline CH); Dioxide CH_2 peak disappears after 1 day on standing at RT in the dark; the imidazolidin-2-one CH_2 peak remains unchanged; MS

shows presence of thiosulfinate which could arise due to the condensation of the dioxide: *m/z* (FAB) 219 (thiosulfinate$^+$, 10%), 150 (dioxide$^+$, 5) and 135 (trioxide$^+$, 5).

b) Non-catalytic conditions – ethanol

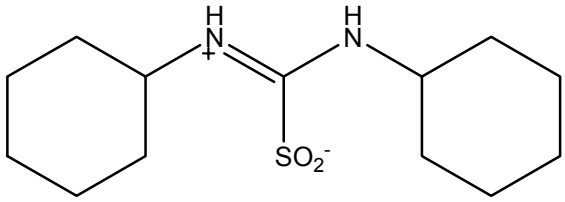
Following a literature procedure,[53] 30% hydrogen peroxide (3 ml, 13 equiv.) was added drop wise to a suspension of ethylenethiourea (204 mg, 2 mmol) in ethanol (20 ml) cooled over an ice-salt bath. The reaction was stirred for 1½ h until the starting material was consumed as determined by TLC. The resultant colourless solution was concentrated under a stream of nitrogen to remove the ethanol. An aliquot of the aqueous layer tested negative for dithionite ions. ^{1}H NMR spectroscopic data was consistent with literature data;[53] the sample was found to contain signals which correspond to the trioxide, 2-imidazoline and imidazolidin-2-one species. No dioxide could be identified. δ_H(300 MHz; D_2O; 1,4-dioxane) 3.51 (0.1H, s, imidazolidin-2-one CH_2), 3.93 (1H, s, 2-imidazoline CH_2) and 4.08 (0.2H, s, trioxide CH_2), 8.15 (0.2H, s, 2-imidazoline CH).

c) **Non-catalytic conditions – carbon tetrachloride**

Following a literature procedure,[28] 30% hydrogen peroxide (0.34 ml, 3 equiv.) was added to an ice-cooled suspension of ethylenethiourea (102 mg, 1 mmol) in carbon tetrachloride (3 ml). The mixture was stirred under a nitrogen atmosphere for 15 min at 0 ºC. The mixture was filtered and washed with methanol to afford a white powder (60 mg). ^{1}H NMR spectroscopic data consistent with literature data[53] and demonstrated the presence of a mixture of the corresponding dioxide and trioxide derivatives. The crude sample tested positive for dithionite ions. ν_{max}(neat)/cm^{-1} 1599, 1558 (C=N) and 1222, 1088, 1060, 1008 (SO_2 and SO_3); δ_H(300 MHz; D_2O; 1,4-dioxane) 3.50 (s, <0.1H, imidazolidin-2-one CH_2), 3.93 (s, 1H, 2-imidazoline CH_2), 4.00 (s, 8H, dioxide CH_2), 4.07 (s, 17H, trioxide CH_2), 2-imidazoline amidine-CH not detected; *m/z* (FAB) 151 (trioxide$^+$ - H, 10%), 135 (dioxide$^+$ - H, 7); Sample left to stand for 2 d at RT and NMR spectrum found to have changed; δ_H(300 MHz; D_2O; 1,4-dioxane) 3.23 (0.6H, t, *J* 6.0, unknown), 3.51

(0.1H, s, imidazolidin-2-one CH_2), 3.62 (0.6H, t, *J* 6.0, unknown), 3.93 (1H, s, 2-imidazoline CH_2), 4.08 (1H, s, trioxide CH_2), 2-imidazoline amidine-CH not detected.

***N,N'*-Dicyclohexylthiourea dioxide 17**



a) Synthesis under non-catalytic conditions

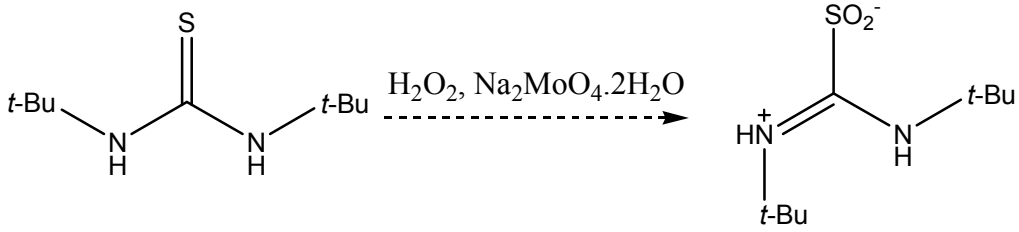
Following a literature procedure,[53] *N,N*'-dicyclohexylthiourea (1 g, 4.2 mmol) was dissolved in hot methanol (20 cm^3) and cooled to RT at which point some precipitate had formed. 30% aqueous hydrogen peroxide (4 ml) was added drop wise to the suspension, under a nitrogen atmosphere, maintaining the temperature at 15 °C. More precipitate had subsequently formed but later partially dissolved after 20 min. The remaining 30% hydrogen peroxide (2 ml, *in toto* 12.9 equiv.) was added as before and the reaction mixture left to stir under a nitrogen atmosphere at 5 °C for 1 h. The suspension was filtered and washed with ice cold methanol to afford a white powder (755 mg, 66%) identified as the title compound **17**, in agreement with literature data.[53] 147-151 °C (Found C, 57.20; H, 8.90; N, 10.30. $C_{13}H_{24}N_2O_2S$ requires C, 57.32; H, 8.88; N, 10.28%); ν_{max}(neat)/cm^{-1} 2927 (NH), 1650 (C=N), 1097 and 1083 (ν_{as} SO_2), 1003 (ν_s SO_2); **17** was found to be insoluble in NMR solvents and appears to degrade on heating, therefore NMR spectroscopic data is unavailable; *m/z* (EI) 208 (M^+ - SO_2, 16%).

b) Synthesis under catalytic conditions

Following a literature procedure,[58] a 250 ml three-necked flask was charged with *N,N'*-dicyclohexylthiourea (1.44 g, 6 mmol), sodium molybdate dihydrate (15 mg, 1 mol%), 1,4-dioxane (25 ml) and diethyl ether (25 ml) and cooled to 2 °C under a nitrogen

atmosphere. 30% aqueous hydrogen peroxide (1.35 ml, 1.8 equiv.) was added drop wise, maintaining the temperature at 2 °C and the reaction mixture left to stir under a nitrogen atmosphere at 2 °C. The suspension was filtered and washed with ice-cold methanol to afford a white powder (699 mg, 43%) identified as the title compound **17**, in agreement with (a) non-catalytic product. 148-150 °C (Found C, 57.86; H, 8.87; N, 10.33. $C_{13}H_{24}N_2O_2S$ requires C, 57.32; H, 8.88; N, 10.28%).

***N,N'*-Di-*tert*-butylthiourea dioxide 18**

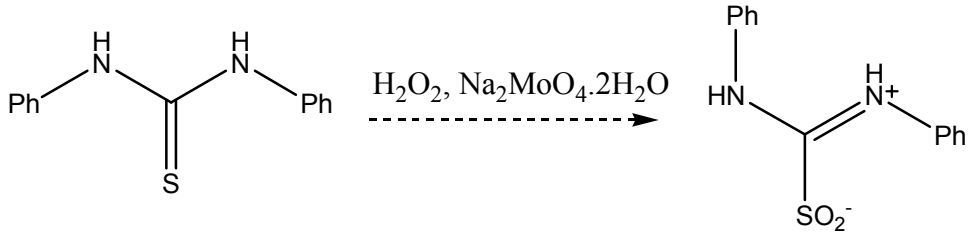


Attempts to isolate the dioxide **18** by following the literature route[58] failed: 30% hydrogen peroxide (0.45 ml, 2 equiv.) was added to a flask charged with *N,N'*-di-*tert*-butylthiourea (377 mg, 2 mmol, recrystallised from acetone/petroleum ether 40:60), sodium molybdate dihydrate (4 mg, 1 mol%), 1,4-dioxane (10 ml) and diethyl ether (10 ml) cooled to 3 ºC and stirred under a nitrogen atmosphere for 3 h. The resultant suspension was filtered and washed with diethyl ether to furnish a white powder (356 mg) which tested negative for dithionite ions. Elemental analysis revealed that the product was not the corresponding thiourea dioxide but either *N,N'*-di-*tert*-butylthiourea trioxide monohydrate or *N,N'*-di-*tert*-butylformamidinium bisulfate (Found C, 42.88; H, 8.74; N, 10.32. Formamidinium bisulfate salt $C_9H_{22}N_2O_4S$ requires C, 42.50; H, 8.72; N, 11.01%); ν_{max}(neat)/cm^{-1} 3219 (NH), 3057-2970 (CH), 1698 (C=N), 1151, 1057 and 1034 (SO_3 stretching); δ_H(300 MHz; DMSO; Me_4Si) 1.31 (18H, br s, CH_3), 7.86 (1H, br t, *J* 13.5, CH, HMQC NMR experiment verifies ^1H-^{13}C coupling with ^{13}C at 151.8 ppm), 9.30 (2H, br d, *J* 13.5, NH, exchangeable with D_2O, leading to a change in multiplicity for ^1H 7.86

ppm: [br t] changes to [br m]); δ_C(75 MHz; DMSO; Me_4Si) 28.9 (CH_3), 53.9 (C_q) and 151.8 (CH).

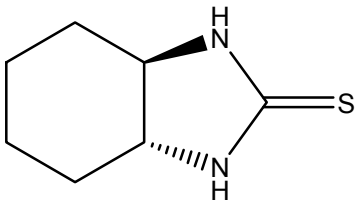
The synthesis of dioxide **18** using non-catalytic conditions[53] furnished a product identical (as judged by NMR spectroscopy) to the sample obtained using the above catalytic conditions.

***N,N'*-Diphenylthiourea dioxide 19**



Attempts to isolate the dioxide **19** by following the literature route[58] failed: 30% hydrogen peroxide (0.45 ml, 2 equiv.) was added to a flask charged with *N,N'*-diphenylthiourea (457 mg, 2 mmol, recrystallised from ethanol), sodium molybdate dihydrate (4 mg, 1 mol%), 1,4-dioxane (10 ml) and diethyl ether (10 ml) cooled to 3 ºC and stirred under a nitrogen atmosphere for 3 h. The resultant suspension was filtered and washed with water to furnish a white solid (187 mg) which tested negative for dithionite ions. The product mixture was thought to contain a formamidinium salt, as deduced by NMR spectroscopy. All characterisation data supplied are for the crude product mixture. Elemental analysis revealed an impure product. (Found C, 58.16; H, 5.07; N, 10.46; S, 7.69. *N,N'*-Diphenylformamidinium bisulfate $C_{13}H_{14}N_2O_4S$ requires C, 53.05; H, 4.79; N, 9.52; S, 10.89%); ν_{max}(neat)/cm^{-1} 1694 (C=N), 1141-1093 (SO_3 or SO_2 stretching), 1024 (ν_s SO_2); δ_H(300 MHz; DMSO; Me_4Si) 7.18-7.64 (10H, br m, ArH), 9.17 (1H, br s, amidine CH, HMQC NMR verified coupling with ^{13}C at 151.7 ppm); δ_C(75 MHz; DMSO; Me_4Si) 119.3, 126.5, 129.6 (3xCH), 136.8 (C_q) and 151.7 (CH).

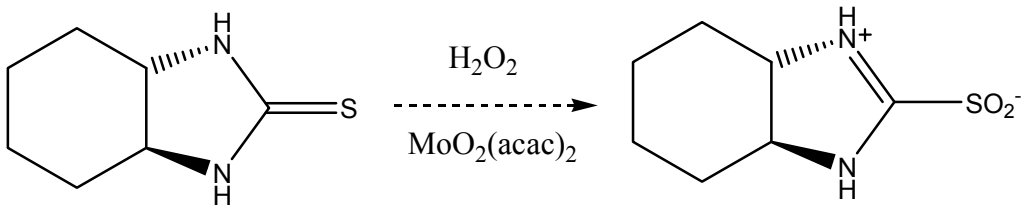
trans-4,5-Tetramethyleneimidazolidin-2-thione 22



Following a literature procedure,[123] a three-necked flask was charged with *trans*-1,2-diaminocyclohexane (10 ml, 100 mmol), water (24 ml) and ethanol (24 ml) and fitted with a water condenser. Carbon disulfide (1.4 ml) was added at the top of the condenser, the reaction flask heated over an oil bath (oil temperature 80 ºC) and the remainder of the carbon disulfide (5.6 ml, 1.16 equiv. *in toto*) added drop wise. The mixture was heated to reflux (oil temperature 100 ºC) for 2 h. 5 M hydrochloric acid (1 ml) was added at the top of the condenser and yellow reaction mixture refluxed for 18 h. The mixture was then cooled in an ice bath, filtered and washed with ice cold ethanol to afford buff crystalline flakes (5.51 g, 35%) identified as the title compound, in agreement with literature data.[123] 200-202 ºC (lit.[123] 148-150 ºC); (Found C, 53.66; H, 7.63; N, 17.84. $C_7H_{12}N_2S$ requires C, 53.81; H, 7.76; N, 17.94%); ν_{max}(neat)/cm^{-1} 3206 (NH), 2935 and 2858 (CH); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.27-1.51 (4H, m, Cy-H), 1.70-1.83 (2H, m, Cy-H), 2.03-2.07 (2H, m, Cy-H), 3.27-3.30 (2H, m, C*H*N), 6.62 (2H, br s, NH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 24.1, 29.3 (2xCH_2), 65.1 (CH) and 187.5 (C=S); *m/z* (ESI) 157 (MH^+, 100%).

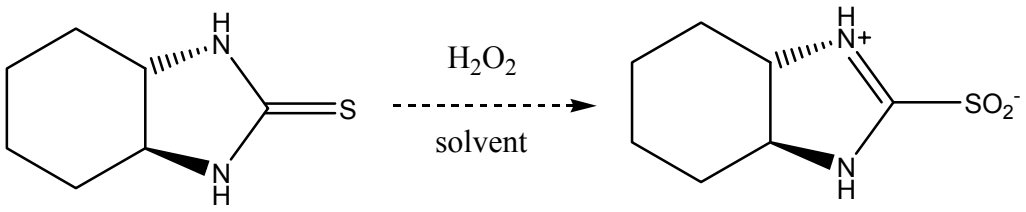
***trans*-4,5-Tetramethyleneimidazolidine-2-sulfinic acid 23**

a) Preparation *via* catalytic conditions



Following a literature procedure,[1] a three-necked flask was charged with *trans*-4,5-tetramethyleneimidazolidin-2-thione **22** (2.1 g, 13.5 mmol), bis(acetylacetonato)dioxomolybdenum(VI) (47 mg, 1 mol%), 1,4-dioxane (50 ml) and diethyl ether (80 ml) and cooled to -5 ºC. 30% hydrogen peroxide (3 ml, 1.8 equiv.) was then added drop wise and the reaction mixture stirred under a nitrogen atmosphere for 35 min maintaining a temperature of -5 ºC. The resultant white suspension was filtered under a nitrogen atmosphere and washed with ice-cold dichloromethane to afford a blue-green powder. The precipitate tested positive for dithionite ions. The IR spectrum of the precipitate showed peaks characteristic of sulfinic acids however the NMR spectrum was too complex to assign. Precipitate: ν_{max}(neat)/cm^{-1} 1078 (ν_{as} SO_2), and 1001 (ν_s SO_2); The filtrate was concentrated *in vacuo* to a blue gum and thought to contain starting thiourea and the corresponding urea (1 : 1 by ^{1}H NMR, comparing between both sets of C*H*NH and CHN*H* integrals) and no dithionite ions were detected. Filtrate: ν_{max}(neat)/cm^{-1} 1691 (C=O); δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.12-3.18 (2H, m, C*H*NH, urea), 3.27-3.33 (2H, m, C*H*NH, thiourea), 4.78 (2H, br s, NH, urea), 6.32 (2H, br s, NH, thiourea). Apparent urea and thiourea cyclohexane ring signals overlap and too complex.

b) General procedure for the preparation of dioxide 23 under non-catalytic conditions



Following a literature procedure,[53] *trans*-4,5-tetramethyleneimidazolidin-2-thione (800 mg, 4.2 mmol) was dissolved in the solvent (10 ml) and cooled to 5 ºC over an ice bath. 30% hydrogen peroxide (1 ml) was added under a nitrogen atmosphere keeping the temperature constant. An aliquot of the reaction mixture tested positive for dithionite ions. The remaining 30% hydrogen peroxide (5 ml, 12.9 equiv. *in toto*, total addition complete after 10 min) was added drop wise; the addition was accompanied with a mild exotherm with the ice-bath still in place. Further aliquots taken tested negative for dithionite ions. The reaction was stirred under a nitrogen atmosphere. The resultant solution was extracted with dichloromethane and the organic layer concentrated *in vacuo*. The aqueous layer was analysed without further manipulation. Both dichloromethane and aqueous layers gave complex ^{1}H NMR spectra.

i. When ethanol or tetrahydrofuran were employed as solvents (reaction time 30 min) following the general procedure, a complex mixture of products was formed and could not be identified by NMR spectroscopy.

ii. When acetonitrile was employed as the solvent, the reaction was accompanied by a temperature rise from 5-8 ºC on addition of hydrogen peroxide; total reaction time 1 h.

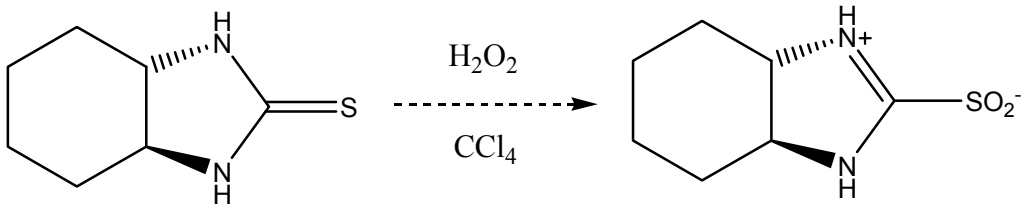
- Dichloromethane extract: ν_{max}(neat)/cm^{-1} 3200-3070 (br, NH), 2941-2868 (CH), 1736, 1692 (C=O, C=N); δ_H(300 MHz; $CDCl_3$; Me_4Si) The

corresponding urea, *trans*-4,5-tetramethyleneimidazolidin-2-one **24**, was detected when the characterisation data was compared with literature values:[123] 1.20–1.60 (4H, m, Cy-H), 1.81–1.83 (2H, m, Cy-H), 1.95-1.98 (2H, m, Cy-H), 3.14-3.17 (2H, m, CHN), 4.58 (br s, apparent 1H, NH); δ_H(300 MHz; D_2O) too complex to interpret, singlet at 8.10 ppm thought be indicative of a formamidinium salt; δ_C(75 MHz; $CDCl_3$; Me_4Si) signals too weak to interpret; δ_C(75 MHz; D_2O) 23.8, 28.4, 29.1, 31.0 (4xCH_2) and 159.8 (CH).

- Aqueous extract: ν_{max}(neat)/cm^{-1} 2943-2864 (CH), 1692 (C=N), 1537, 1090, 1040; δ_H(300 MHz; D_2O) too complex to assign, singlet at 8.10 ppm; δ_C(75 MHz; D_2O) 22.7, 23.2, 23.6, 29.2, 29.5, 30.6 (6xCH_2), 52.1, 52.5 and 53.5 (3xCH).

iii. When 1,4-dioxane was employed as a solvent, the crude product was thought to be the corresponding urea, *trans*-4,5-tetramethyleneimidazolidin-2-one **24**, as determined by IR and NMR spectroscopic analyses when compared with (ii) acetonitrile conditions. Near-IR spectroscopy monitoring was employed, using 1,4-dioxane as a solvent. The near-IR spectrum is included in the appendix.

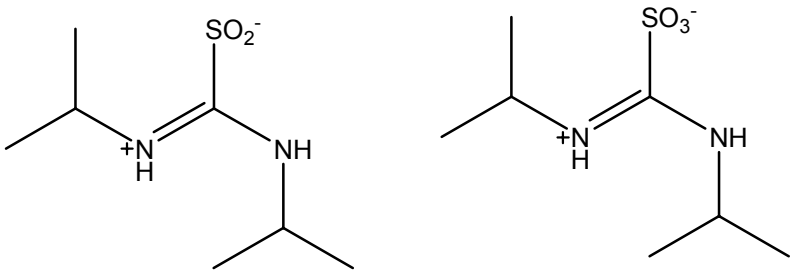
c) Preparation *via* non-catalytic hydrogen peroxide oxidation in carbon tetrachloride



Following a literature procedure,[28] 30% hydrogen peroxide (0.34 ml, 3 equiv.) was added to a suspension of *trans*-4,5-tetramethyleneimidazolidin-2-thione **22** (156 mg, 1 mmol) in

carbon tetrachloride (3 ml) at RT. After stirring for 40 min, the suspension was filtered and washed with carbon tetrachloride to afford a white powder (80 mg) which tested positive for dithionite ions. The sample was still impure (as deduced by elemental analysis) but represented the best result, in this thesis, with regard to isolating dioxide **23**. 136-138 °C (Found C, 42.03; H, 6.14; N, 13.92; S, 16.52. $C_7H_{12}N_2O_2S$ requires C, 44.66; H, 6.43; N, 14.87; S, 17.03%); ν_{max}(neat)/cm^{-1} 3567 (NH or OH), 3191, 2941-2866 (CH), 1558-1512 (C=N), 1251, 1228, 1053 and 1033 (SO_2 and SO_3); δ_H(300 MHz; DMSO; Me_4Si) 1.20-1.40 (3H, br m, Cy-H), 1.43-1.61 (2H, br m, Cy-H), 1.62-1.85 (3H, br m, Cy-H), 3.45-3.60 (2H, br m, Cy-H), 8.31 and 8.62 (s, integration not possible but could represent formamidinium CH signals; peaks appear to increase in intensity after 4 days at RT in the light), 10.00-11.00 (2H, br m, NH, peak resolves to two broad singlets 10.40-11.00 and integrates to two protons after 4 days); δ_C(75 MHz; DMSO; Me_4Si) 23.3, 23.4, 28.0, 28.3 (4xCH_2), 65.1 and 170.9 (2xCH); *m/z* (ESI) 173 (M^+ - O, 80%).

***N,N'*-Diisopropylthiourea dioxide 25 and *N,N*-diisopropylthiourea trioxide 27**



25 **27**

Following a literature procedure,[1] a 250 ml three-necked flask was charged with *N,N*'-diisopropylthiourea (2.16 g, 13.5 mmol), bis(acetylacetonato)dioxomolybdenum(VI) (47 mg, 1 mol%), 1,4-dioxane (30 ml) and diethyl ether (40 ml) and cooled to -5 °C. 30% aqueous hydrogen peroxide (3.36 ml, 2 equiv.) was added drop wise to the suspension maintaining the temperature at -7 °C. The reaction mixture was stirred under a nitrogen atmosphere at -5 °C for 1 h. The yellow precipitate was filtered and washed under a

blanket of nitrogen with 1,4-dioxane and diethyl ether to afford a fine white powder identified as *N,N'*-diisopropylthiourea dioxide **25** (2.04 g, 79%) which tested positive for dithionite ions. 123-124 ºC (Found C, 43.32; H, 8.28; N, 14.36. $C_7H_{16}N_2O_2S$ requires C, 43.73; H, 8.39; N, 14.57%); ν_{max}(neat)/cm^{-1} 1651 (C=N), 1080 (ν_s SO_2) and 1009 (ν_s SO_2); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.25 (6H, d, *J* 6.4, Me), 1.35 (6H, d, *J* 6.4, Me), 4.05 (1H, m, CH), 4.65 (1H, m, CH), 7.50 (1H, m, NH), 8.65 (1H, m, NH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 22.2, 23.5 (2xCH_3), 44.3, 46.9 (2xCH) and 171.3 (CS); *m/z* (ESI) 193 (MH^+, 89%) and 129 (MH^+ - SO_2, 65).

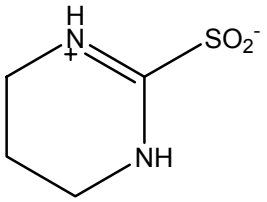
The filtrate was left to stand at RT overnight with the formation of colourless crystals (70 mg, 3%). The product was identified as *N,N'*-diisopropylthiourea trioxide **27** and tested negative for dithionite ions. 185-186 °C (Found C, 40.08; H, 7.73; N, 13.40; S, 15.42. $C_7H_{16}N_2O_3S$ requires C, 40.37; H, 7.74; N, 13.45; S, 15.39%); ν_{max}(neat)/cm^{-1} 3222 (NH), 2983 (CH), 1645 (C=N) and 1231, 1140 (ν_{as} SO_3), 1051 (ν_s SO_3); δ_H(300 MHz; DMSO; Me_4Si) 1.20 (6H, d, *J* 6.3, CH_3), 1.24 (6H, d, *J* 6.3, CH_3), 3.87 (1H, m, CH), 4.71 (1H, m, CH), 8.65 (1H, m, NH), 8.70 (1H, m, NH); D_2O shake results in NH to ND exchange; δ_C(75 MHz; DMSO; Me_4Si) 21.0, 22.6 (2xCH_3), 44.7, 48.1 (2xCH) and 161.3 (CS); *m/z* (ESI) 206 (M^- - H, 95%).

Crystal structure analysis of 25

Single crystals of *N,N'*-diisopropylthiourea dioxide $C_7H_{16}N_2O_2S$ were grown from ethanol/acetonitrile (-20 ºC) and mounted in an inert oil and transferred to the cold gas stream (Oxford Cryosystems 700) on a Bruker-AXS SMART three circle area detector diffractometer system equipped with $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). Data were collected with narrow (0.3 ° in ω) frame exposures. Intensities were corrected semi-empirically for absorption, based on symmetry-equivalent and repeated reflections (SADABS). Structures were solved by direct methods (SHELXS)[201] with additional light atoms found by Fourier methods. All non hydrogen atoms were refined anisotropically. H

atoms were constrained with a riding model ; U(H) was set at 1.2 (1.5 for methyl groups) times U_{eq} for the parent atom except the NH hydrogens which were located in a difference map and their position allowed to refine but their U(H) was set at 1.5 times U_{eq} for the parent atom. Programs used were Bruker AXS SMART (control), SAINT (integration) and SHELXTL[201] for structure solution, refinement, and molecular graphics.

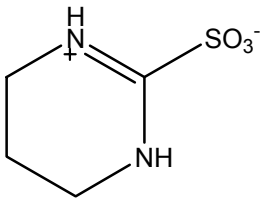
Propylenethiourea dioxide 26



Following a literature procedure,[1] a 250 ml three-necked flask was charged with propylenethiourea (1.04 g, 9 mmol), bis(acetylacetonato)dioxomolybdenum(VI) (30 mg, 1 mol%), 1,4-dioxane (30 ml) and diethyl ether (40 ml) and cooled to -5 °C under a nitrogen atmosphere. 30% aqueous hydrogen peroxide (2.24 ml, 2 equiv.) was added drop wise to the suspension maintaining the temperature at -5 °C. The reaction mixture was stirred under a nitrogen atmosphere at -5 °C for 3 h. The resultant yellow precipitate[a] was filtered under a nitrogen atmosphere. The resultant white precipitate was washed with chloroform and the filtrate concentrated *in vacuo* to afford a white powder (100 mg, 7%) identified as the title compound. 133-134 ºC (Found C, 32.26; H, 5.37; N, 18.58. $C_4H_8N_2O_2S$ requires C, 32.42; H, 5.44; N, 18.90%); ν_{max}(neat)/cm^{-1} 1653 (C=N), 1094 (ν_{as} SO_2), 989 (ν_s SO_2), 965; δ_H(300 MHz; D_2O; CH_3CN) 1.98 (2H, quintuplet, J 5.7, $CH_2CH_2CH_2$), 3.50 (4H, m, NCH_2); δ_C(75 MHz; D_2O; CH_3CN) 16.8, 38.2 (2xCH_2), CS not observed; *m/z* (ESI) 149 (MH^+, 30%).

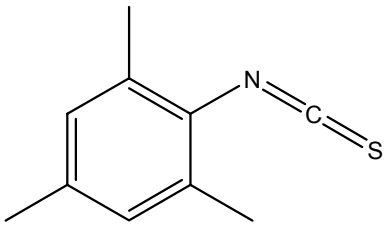
[a] 1.62 g propylenethiourea scale experiment produces blue-green oil which, on work-up, affords **26**

Propylenethiourea trioxide 28



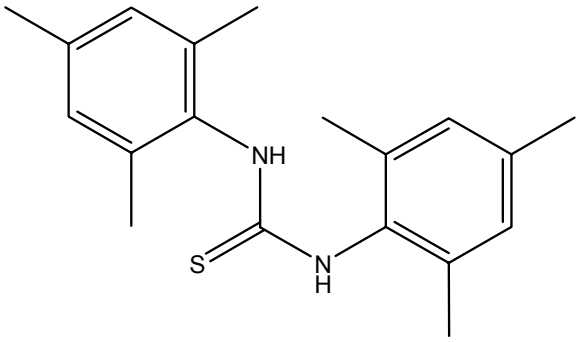
Following a literature procedure,[1] 30% hydrogen peroxide (2.88 ml, 2 equiv.) was added drop wise to a suspension of propylenethiourea (1.62 g, 14 mmol) and sodium molybdate dihydrate (34 mg, 1 mol%) in 1,4-dioxane (30 ml) and diethyl ether (40 ml) cooled to -5 ºC under a nitrogen atmosphere. The mixture was stirred for 3 h maintaining the temperature at -5 ºC. The resultant blue-green oily suspension was filtered through a celite pad and washed with 10% methanol/dichloromethane solution. The filtrate was then concentrated *in vacuo* to afford a pale blue-green solid (*ca.* 6.6 g). Purification was achieved by flash chromatography (silica, 50 g) with 1:1:3 methanol:acetonitrile:dichloromethane to afford white flakes (450 mg, 20%) identified as propylenethiourea trioxide. The product tested negative for dithionite ions. 280 °C (decomp.) (Found C, 29.31; H, 4.88; N, 16.66; S, 19.56; $C_4H_8N_2O_2S$ requires C, 29.26; H, 4.91; N, 17.06; S, 19.53%); ν_{max}(neat)/cm^{-1} 3263-3134 (NH), 2988 (CH), 1673 (C=N) and 1229 (ν_{as} SO_3), 1083 and 1040 (ν_s SO_3); δ_H(400 MHz; D_2O; 1,4-dioxane) 1.90 (2H, m, $CH_2CH_2CH_2$), 3.42 (4H, t, *J* 5.8, $NHCH_2$); δ_C(75 MHz; D_2O; 1,4-dioxane) 17.2, 38.9 (2xCH_2) and 160.1 (CS); MS ESI gave no identifiable ions or fragments.

_N_-Mesitylisothiocyanate 29



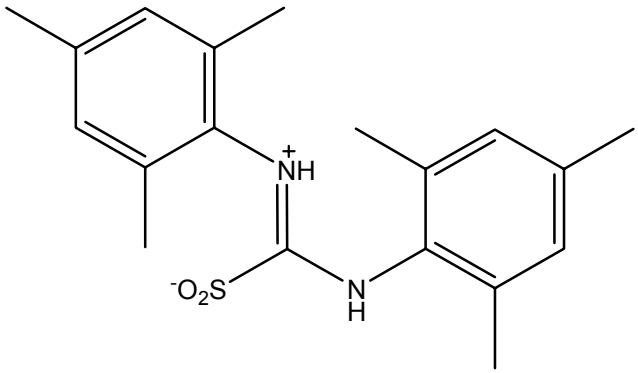
Following a literature procedure,[128] thiocarbimidazole (2.49 g, 2 equiv.) in anhydrous acetonitrile (50 ml) was added drop wise to a solution of mesitylamine (0.98 ml, 7 mmol) in anhydrous acetonitrile (100 ml) cooled at 0 ºC. After *ca.* 15 min (for addition), the reaction mixture was stirred at RT under a nitrogen atmosphere for 4 h. The reaction was quenched with water, partitioned over dichloromethane and separated. The aqueous layer was extracted with dichloromethane. All organic solutions were combined, dried (sodium sulfate), filtered and concentrated *in vacuo* to an orange solid. Purification of the crude material using flash chromatography (silica, 40 g) with 1:1 diethyl ether: petroleum ether 40:60 afforded an orange solid (1.27 g, quantitative) identified as the required isothiocyanate, in agreement with literature data.[128] 62-63 ºC; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.25 (3H, s, *para*-CH_3), 2.32 (6H, s, *ortho*-CH_3), 6.83 (2H, s, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 18.0, 20.5 (2xCH_3), 126.2 (C_q), 128.1 (CH), 134.2, 136.4 (2xC_q), CS not observed; *m/z* (EI) 177 (M^+, 100%).

***N,N'*-Dimesitylthiourea 30**



Following a literature procedure,[128] a mixture of mesitylisothiocyanate **29** (1.26 g, 7.1 mmol), mesitylamine (5.16 ml, 5.2 equiv.) and toluene (100 ml) was heated to reflux for 4 d. The mixture was cooled to RT and the toluene removed *in vacuo*. The resultant oily orange suspension was recrystallised twice from ethyl acetate/petroleum ether (40:60) to afford a fibrous white solid. Further purification using flash chromatography (silica, 15 g, dry-load with methanol) using petroleum ether (40:60) to diethyl ether furnished a white solid (576 mg, 26%) identified as the required thiourea, in agreement with literature data.[128] 201-205 ºC; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.18 (6H, s, *ortho*-CH_3), 2.24 (3H, s, *para*-CH_3), 2.30 (3H, s, *para*-CH_3), 2.38 (6H, s, *ortho*-CH_3), 6.50 (1H, br s, NH), 6.86 (1H, s, ArH), 7.00 (1H, s, ArH), 7.48 (1H, br s, NH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 17.7, 18.0, 20.4 (3xCH_3), 128.5, 129.2 (2xCH), 129.9, 132.5, 135.5, 136.7, 137.2, 138.6 (6xC_q) and 180.74 (C=S); *m/z* (EI) 312 (M^+, 15%).

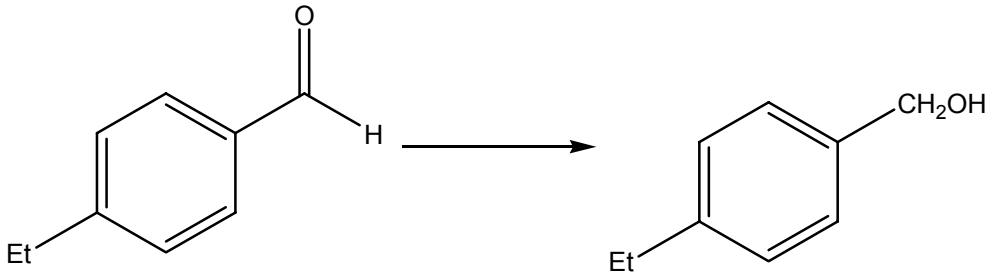
_N,N_'-Dimesitylthiourea dioxide 31



Following a literature procedure,[1] a three-necked flask was charged with *N,N'*-dimesitylthiourea **30** (200 mg, 0.64 mmol), bis(acetylacetonato)dioxomolybdenum(VI) (2 mg, 1 mol%), 1,4-dioxane (3 ml) and diethyl ether (3 ml) and cooled to -5 ºC. 30% hydrogen peroxide (0.15 ml, 2 equiv.) was added and the reaction stirred at -5 ºC under a nitrogen atmosphere for 1½ h. The resultant suspension was filtered and washed with diethyl ether and dried (40 ºC, 0.4 mbar) to afford a white solid (131 mg, 60%) identified as *N,N*'-dimesitylthiourea dioxide, as judged by IR spectroscopy and high-resolution mass spectrometry. Elemental analysis revealed an impure product. 204-205 °C (Found C, 65.32; H, 7.01; N, 7.99; S, 8.20. $C_{19}H_{24}N_2O_2S$ requires C, 66.25; H, 7.02; N, 8.13; S, 9.31%); ν_{max}(neat)/cm^{-1} 1624 (C=N), 1104 (ν_{as} SO_2) and 1008 (ν_s SO_2); δ_H(300 MHz; DMSO; Me_4Si) 2.10 (6H, s, *ortho*-CH_3), 2.18 (6H, s, *ortho*-CH_3), 2.22 (3H, s, *para*-CH_3), 2.26 (3H, s, *para*-CH_3), 6.90 (2H, s, ArH), 7.01 (2H, s, ArH); δ_C(75 MHz; DMSO; Me_4Si) 17.0, 18.2, 20.6 (3xCH_3), 128.5 (CH), 129.0 (C_q), 129.2(CH), 135.0, 135.4, 137.4, 137.7 (4xC_q, missing one aromatic-C_q), CS not observed; *m/z* (LSIMS) 345 (MH^+, 20%) and 271 (MH^+ - SO_2, 100); HRMS (LSIMS) 345.1624, $C_{19}H_{25}N_2O_2S$+H requires 345.1637.

Chapter 3 experimental

General procedure for the reduction of 4-ethylbenzaldehyde 32



A scintillation vial was charged with 4-ethylbenzaldehyde **32** (0.27 ml, 2 mmol), 3 M sodium hydroxide (2.67 ml, 4 equiv.), ethanol (4 ml) and the reducing agent and then heated to 78 ºC for 4 h. The reaction was quenched with 2 M hydrochloric acid, partitioned over dichloromethane and separated. The organic layer was dried (sodium sulfate), filtered and concentrated *in vacuo* to an off-white solid. The crude material was purified under flash chromatography (silica, 20 g) with *n*-pentane, 10% diethyl ether followed by ethyl acetate to afford a yellow oil. The oil was distilled in a Kugelrohr apparatus (130 ºC, 16 mbar) to afford a colourless liquid identified as 4-ethylbenzylalcohol **33**, when compared with an authentic sample.

a) Thiourea dioxide **3** (432 mg, 2 equiv.) following the general procedure furnished the alcohol **33** (232 mg, 85%).

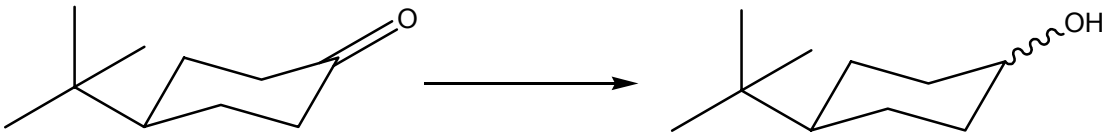
b) *N,N*'-Diisopropylthiourea dioxide **25** (769 mg, 2 equiv.) following the general procedure gave the alcohol **33** (147 mg, 54%).

Spectroscopic data. ν_{max}(neat)/cm^{-1} 3317 (OH), 2964-2872 (CH), 1007 (C-O); δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.23 (3H, t, *J* 7.6, CH_3), 1.82 (1H, br s, OH), 2.64 (2H, quartet, *J* 7.6, C*H*$_2$CH$_3$), 4.65 (2H, s, C*H*$_2$OH), 7.19 (2H, AA' of AA'BB', *J* 8.0, ArH), 7.26 (2H, BB' of AA'BB', *J* 8.0, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 15.7 (CH_3), 28.6, 65.3

($2xCH_2$), 127.2, 128.1 (2xCH), 138.2 and 143.9 ($2xC_q$); *m/z* (EI) 136 (M^+), 107 (M^+ - CH_2CH_3).

Attempts to repeat the above experiment in tetrahydrofuran at 0 ºC and 65 ºC with *N,N*'-diisopropylthiourea dioxide **25**, to encourage the formation of the corresponding pinacol, were unsuccessful. A sample of the crude reaction mixture at 0 ºC was found to contain *N,N*'-diisopropylurea, starting aldehyde and unknown compounds by NMR spectroscopy. A sample of the crude reaction mixture at 65 ºC was found to contain the starting aldehyde and a complex mixture of unknown compounds as judged by NMR spectroscopy.

General procedure for the reduction of 4-*tert*-butylcyclohexanone



4-*tert*-Butylcyclohexanone (463 mg, 3 mmol) was added to a solution of the thiourea dioxide and sodium hydroxide in ethanol (6 ml) and water (4 ml) and heated to 78 ºC under a nitrogen atmosphere for 4 h. The reaction mixture was cooled to RT and acidified with 2 M hydrochloric acid. The white suspension was partitioned over diethyl ether, filtered and separated. The aqueous layer was extracted with diethyl ether and all organic media combined, dried (sodium sulfate), filtered and concentrated to an off-white solid. Purification was achieved *via* flash chromatography (silica, 20 g) with *n*-pentane and 10–25% diethyl ether/*n*-pentane to afford the *cis* (**34a**) and the *trans*-diastereoisomers (**34b**) of 4-*tert*-butylcyclohexanol as a white wool.

- Thiourea dioxide **3** (648 mg, 2 equiv.) and sodium hydroxide (480 mg, 4 equiv.) gave the alcohol (211 mg, 45%, 3:97 *cis*:*trans*).

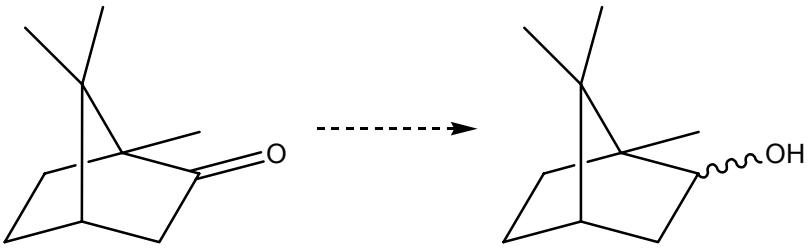
- *N,N'*-diisopropylthiourea dioxide **25** (1.15 g, 2 equiv.) and sodium hydroxide (480 mg, 4 equiv.) gave the alcohol (208 mg, 44%, 4:96 *cis*:*trans*).

Spectroscopic data.[202] ***cis*-4-*tert*-Butylcyclohexanol 34a**: 83–84 ºC; ν_{max}(neat)/cm^{-1} 3320, 3230 (OH), 2951; δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.85 (9H, s, CMe_3), 0.90-1.61 (7H, m, Cy-H), 1.80-1.88 (2H, m, Cy-H), 4.02-4.05 (1H, m, C*H*OH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.3 (CH_2), 27.9 (CH_3), 33.0 (*C*Me_3), 33.8 (CH_2), 48.4 and 66.3 (2xCH); *m/z* (ESI) 158 (MH^-). ***trans*-4-*tert*-Butylcyclohexanol 34b**: 79–80 ºC; ν_{max}(neat)/cm^{-1} 3257 (OH) 2941; δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.85 (9H, s, CMe_3), 0.90-1.41 (5H, m, Cy-H), 1.75-1.83 (2H, m, Cy-H), 2.00-2.06 (2H, m, Cy-H), 3.47-3.57 (1H, m, C*H*OH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 26.0 (CH_2), 28.1 (CH_3), 32.7 (*C*Me_3), 36.5 (CH_2), 47.5 and 71.6 (2xCH); *m/z* (ESI) 158 (MH^-).

Test[79] for Meerwein-Ponndorf reduction of 4-*tert*-butylcyclohexanone

Attempts to repeat the reduction i) without base or ii) without the dioxide **25** resulted in no alcohol formation. Crude samples of the reaction mixture were found to contain, respectively, i) starting ketone and unknown formamidinium-type products (similar to **48**), or ii) starting ketone.

General procedure for the reduction of *1S*-(-)-Camphor



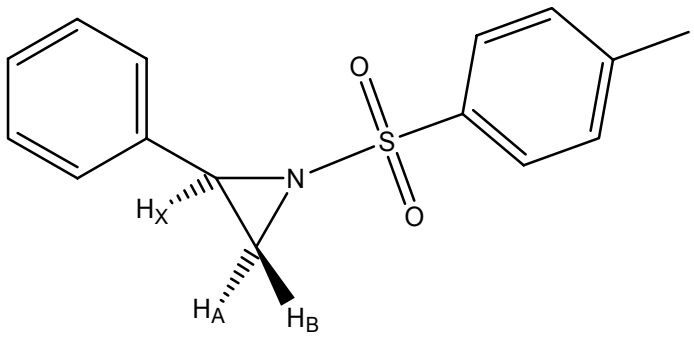
A solution of the reducing agent, 3 M sodium hydroxide (4 ml, 4 equiv.), ethanol (6 ml) and *1S*-(-)-Camphor (457 mg, 3 mmol) were heated in a capped scintillation vial at 78 ºC

for 5 h. The reaction was quenched, partitioned over dichloromethane and separated. The dichloromethane layer was dried (sodium sulfate), filtered and concentrated *in vacuo*.

- Sodium dithionite (522 mg, 1 equiv.) was used following the general procedure and resulted in a white foam, after quenching with saturated ammonium chloride and following the general work-up procedure. Flash chromatography purification (silica, 20 g) using *n*-pentane to 15% diethyl ether/*n*-pentane gave the starting ketone (327 mg, 72% recovery) and an off-white oil (9 mg) which gave a complex ^{1}H and ^{13}C NMR spectra. No borneol **35** (*trans*-alcohol) or isoborneol (*cis*-alcohol) could be identified, when compared with authentic samples.

- *N,N*'-Diisopropylthiourea dioxide **25** (1.15 g, 2 equiv.) gave a red-brown solid after quenching with 2 M hydrochloric acid and following the general work-up procedure. No purification was carried out. Crude samples were found to contain *N,N*'-diisopropylurea **47** and *1S*-(-)-Camphor as the major components by NMR spectroscopy. A minute trace of both *cis* and *trans*-alcohols (C*H*OH multiplet at 3.60 and 4.00, respectively, in d_1-chloroform) were detected in the ^{1}H NMR spectrum (compared with authentic samples) although integration was not possible.

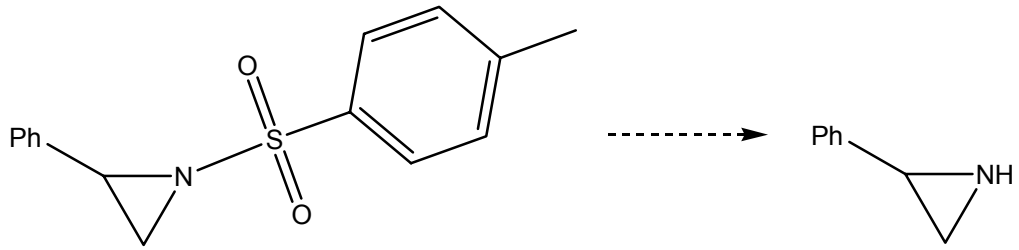
2-Phenyl-*N*-tosylaziridine 36



Following procedures developed in our group, a Schlenk tube was charged with chloramine-T trihydrate (423 mg, 1.5 equiv.), phenanthroline (18 mg, 0.1 equiv.), copper(I) iodide (19 mg, 0.1 equiv.) and acetonitrile (7 ml) and stirred under a nitrogen

atmosphere for 30 min. Styrene (0.12 ml, 1 mmol) was added to the green mixture. The reaction mixture was sealed and heated over an oil bath (oil temperature 50 ºC) for 5 h. The mixture was cooled to RT, filtered through a celite pad, washed with acetonitrile and the filtrate concentrated *in vacuo* to a yellow-brown wax. The crude material was purified under flash chromatography (15 g silica, neutralised with 10% triethylamine/diethyl ether) using *n*-pentane to 40% ethyl acetate/*n*-pentane to afford a buff wax (126 mg, 46%) identified as 2-phenyl-*N*-tosylaziridine, when compared with an authentic sample. 94–95 ºC; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.36 (1H, d, J_{BX} 4.5, H_B), 2.42 (3H, s, $ArCH_3$), 2.97 (1H, d, J_{AX} 7.2, H_A), 3.76 (1H, dd, J_{BX} 4.5, J_{AX} 7.2, H_X), 7.18-7.33 (7H, m, ArH), 7.84 (2H, BB' of AA'BB', *J* 8.3, MeC_4H_4); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.1 (CH_3), 29.1 (CH_2), 35.3, 40.4, 126.0, 127.3, 127.7, 128.0, 129.2 (6xCH), 134.4 and 144.1 ($2xC_q$); *m/z* (ESI) 297 ($MHNa^+$, 55%) and 273 (M^+, 30).

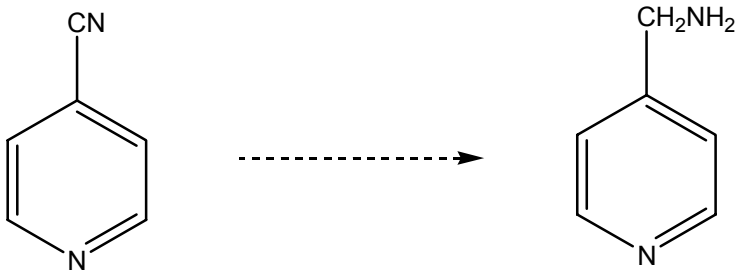
Reduction of 2-phenyl-*N*-tosylaziridine 36 with *N,N*'-diisopropylthiourea dioxide 25



A flask was charged with *N,N'*-diisopropylthiourea dioxide **25** (284 mg, 4 equiv.), 3 M sodium hydroxide (0.5 ml, 4 equiv.) and ethanol (5 ml) and heated under a nitrogen atmosphere over an oil bath (oil temperature 85 ºC) for 10 min. 2-Phenyl-*N*-tosylaziridine **36** (100 mg, 0.37 mmol) in ethanol (10 ml) and a few drops of acetonitrile (to aid solubility) were then added to the reaction mixture and heated for 2½ h. TLC analysis revealed that the reducing agent was consumed. The reaction mixture was cooled to RT, partitioned over brine and dichloromethane and separated. The organic layer was dried (sodium sulfate), filtered and concentrated to a buff solid. Starting aziridine **36** with trace of complex unknown signals, was found by NMR spectroscopy.

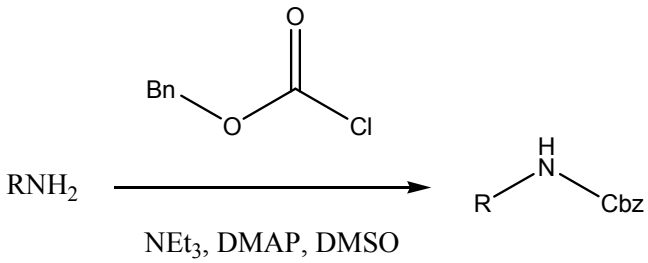
The experiment was repeated twice with lower reducing agent quantity (2 equiv. dioxide **25**, as opposed to 4 equiv.) and also with no reducing agent **25** to test the effect of hydroxide/ethoxide nucleophilic ring-opening. After purifying the control experiments with flash chromatography the products remained unidentifiable and the NMR spectrum was too complex to interpret. GCMS (EI/CI) analysis of the crude mixtures was inconclusive.

Reduction of 4-pyridinecarbonitrile 37 with *N,N*'-diisopropylthiourea dioxide 25



A scintillation vial was charged with 4-pyridinecarbonitrile **37** (208 mg, 2 mmol), *N,N*'-diisopropylthiourea dioxide **25** (769 mg, 2 equiv.), 3 M sodium hydroxide (2.67 ml, 4 equiv.) and ethanol (4 ml) and heated to 78 ºC for 4 h. The reaction was cooled in an ice bath and acidified to pH 2 with 2 M hydrochloric acid and then filtered to remove *N,N*'-diisopropylurea as beige needles. The filtrate was basified to pH 12 with saturated sodium carbonate, partitioned over dichloromethane, separated and the organic layer dried (sodium sulfate). The dichloromethane layer was filtered and concentrated to a bright yellow solid (200 mg). Only *N,N*'-diisopropylurea **47** was found as judged by NMR spectroscopy. The aqueous layer was concentrated *in vacuo* and washed with methanol. The methanol washings were concentrated *in vacuo* to a white solid and found to contain the starting nitrile only.

General procedure[203] for the synthesis of Cbz-protected amines



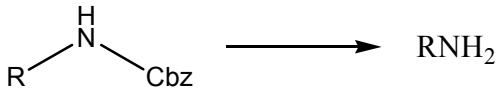
Benzyl chloroformate (2.25 ml, 2.25 equiv.) was added drop wise to a solution of the amine (7 mmol), triethylamine (1.95 ml, 2 equiv.), 4-*N,N*-dimethylaminopyridine (171 mg, 0.2 equiv.) in dimethylsulfoxide (6 ml). The mixture was then heated to 50 ºC under a nitrogen atmosphere for 1.5 h. The mixture was cooled to RT, quenched with sodium bicarbonate (50 ml) and water (100 ml), partitioned over ethyl acetate and separated. The aqueous layer was extracted with ethyl acetate. All organic layers were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. The crude mixtures were then purified under flash chromatography (silica, 20 g) using petroleum ether (40:60) to 50% petroleum ether (40:60)/ethyl acetate to give the required Cbz-amines.

a) Benzylamine (0.76 ml) gave *O,N*-dibenzylcarbamate **38**, in agreement with literature data,[204] as a white solid (416 mg, 25%). 62 – 64 ºC; ν_{max}(neat)/cm^{-1} 3319 (NH), 3063-2927 (CH), 1685 (C=O); δ_H(300 MHz; $CDCl_3$; Me_4Si) 4.35 (2H, m, NHCH_2), 5.03-5.20 (3H, br m, OCH_2 and NH), 7.23-7.42 (10H, m, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 44.5, 66.3 (2xCH_2), 126.9, 127.5, 127.9, 128.1 (4xCH), 135.9 and 137.8 (2xC_q); *m/z* (EI) 241 (M^+, 5%).

b) Piperidine (0.69 ml) gave *N*-carboxybenzylpiperidine **39**, in agreement with literature data,[205] as a colourless oil (805 mg, 52%). ν_{max}(neat)/cm^{-1} 2936-2855 (CH), 1694 (C=O); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.42-1.70 (6H, br m, piperidine 3-H, 4-H and 5-H), 3.40-3.49 (4H, m, piperidine 2-H and 6-H), 5.12 (2H, s, CH_2Ph), 7.26-7.42 (5H,

m, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 23.8, 25.1, 44.2, 66.3 (4xCH_2), 127.2, 127.3, 127.8 (3xCH), 136.4 and 154.7 (2xC_q); *m/z* (EI) 219 (M^+, 13%).

General procedure for the reduction of Cbz-protected amines with *N,N*'-diisopropylthiourea dioxide 25

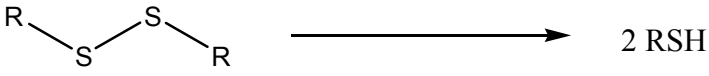


A capped scintillation vial was charged with the carbamate (0.5 mmol), *N,N*'-diisopropylthiourea dioxide **25** (193 mg, 2 equiv.), 3 M sodium hydroxide (0.6 ml, 4 equiv.), ethanol (5 ml) and 1,3,5-tri-*tert*-butylbenzene (20 mg, 0.16 equiv., GC internal standard) and heated to 80 ºC for 4 h. The reaction was cooled to RT and reaction progress followed by GC after 4 h. Column gradient 100-200 ºC at 10 ºC min^{-1} then hold at 200 ºC for 1 min; R_t 1,3,5-tri-*tert*-butylbenzene 9.82 min.

a) *O*,*N*-Dibenzylcarbamate **38** (120 mg) gave benzylamine (R_t 4.90 min) 2.7% conversion.

b) *N*-Carboxybenzylpiperidine **39** (110 mg) resulted in no piperidine formation (R_t 2.88 min).

General procedure[83] for the reduction of disulfides with thiourea dioxide derivatives



A suspension of the disulfide (2.5 mmol), thiourea dioxide derivative (1.8 equiv.), sodium hydroxide (560 mg, 5.6 equiv.) in ethanol (4.5 ml) and water (3 ml) were heated under a nitrogen atmosphere to 78 °C for 3 h. The reaction mixture was cooled to RT and extracted with diethyl ether to remove starting material. The aqueous layer was acidified with 2 M hydrochloric acid, partitioned over diethyl ether and separated. The organic

layer was dried (sodium sulfate), filtered and concentrated to an oil. The crude material was then purified *via* Kugelrohr distillation to afford the desired thiol (when compared with an authentic sample) as a colourless liquid.

a) Reduction of *S,S*'-diphenyldisulfide (R = Ph) to thiophenol **40** (distilled at 80 °C, 16 mbar).

- Thiourea dioxide **3** gave thiophenol **40** (145 mg, 53%)
- *N,N*'-Diisopropylthiourea dioxide **25** gave thiophenol **40** (236 mg, 86%)

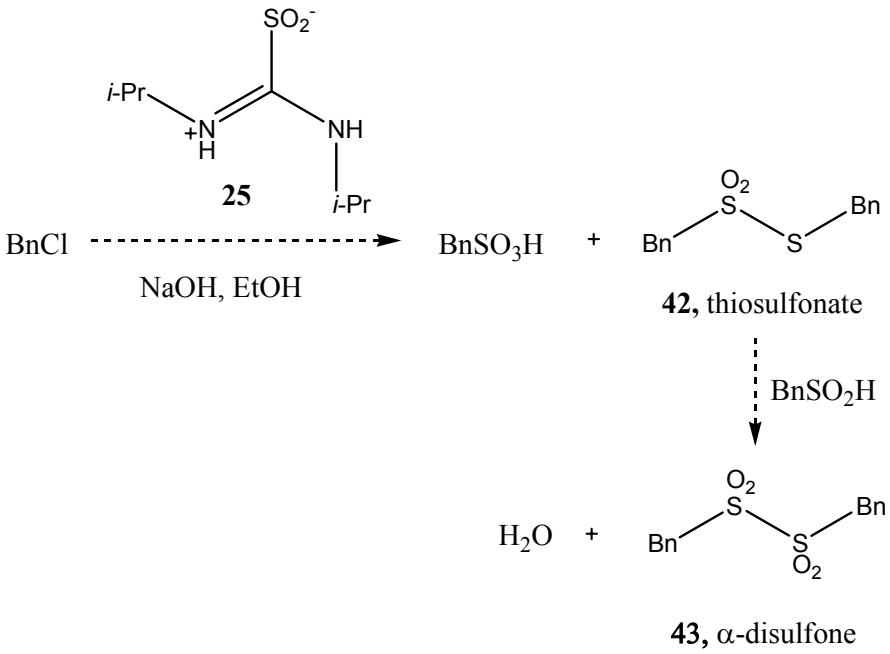
Spectroscopic data of thiophenol **40**. δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.40 (1H, s, SH), 7.10-7.30 (5H, m, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 125.7, 129.1, 129.5 (3xCH) and 130.8 (C_q); *m/z* (EI) 110 (M^+, 100%).

b) Reduction of *S,S*'-dibenzyldisulfide (R = Bn) to benzyl mercaptan **41** (distilled at 86 °C, 16 mbar).

- Thiourea dioxide **3** gave benzyl mercaptan **41** (148 mg, 48%)
- *N,N*'-Diisopropylthiourea dioxide **25** gave benzyl mercaptan **41** (212 mg, 68%)

Spectroscopic data of benzyl mercaptan **41**. δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.75 (1H, t, *J* 7.5, SH), 3.73 (2H, d, *J* 7.5, CH_2), 7.20-7.35 (5H, m, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 29.4 (CH_2), 127.5, 128.5, 129.1 (3xCH) and 141.6 (C_q); *m/z* (EI) 124 (M^+, 20%).

Reaction of benzyl chloride with *N,N*'-diisopropylthiourea dioxide 25



A Schlenk tube was charged with *N,N*'-diisopropylthiourea dioxide **25** (769 mg, 2 equiv.), 3 M sodium hydroxide (2.67 ml, 4 equiv.) and ethanol (4 ml) and heated over an oil bath under a nitrogen atmosphere until the oil temperature reached 40 ºC. Benzyl chloride (0.23 ml, 2 mmol) was then added drop wise to the solution while raising the oil temperature to 65 ºC, resulting in the evolution of white fumes ensuing during addition. The reaction mixture was then stirred under further heating (oil temperature 100 ºC) for 4 h. The reaction was cooled over an ice bath, neutralised with 2 M hydrochloric acid and partitioned over diethyl ether. The layers were separated, organic layer dried (sodium sulfate), filtered and concentrated *in vacuo* to a white solid (800 mg). The crude mixture was purified under flash chromatography (silica, 30 g) using *n*-pentane, 50% *n*-pentane/diethyl ether, ethyl acetate, 10% ethanol/dichloromethane, methanol and 10% ammonium hydroxide/methanol to afford three fractions. No benzyl alcohol was detected.

a) Yellow liquid (91 mg, crude) identified as the thiosulfonate **42** as judged by NMR spectroscopy (when compared with literature data;[206] thiosulfonate peaks italicised).

δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.80-1.45 (3.5H, br m, unknown), 1.90 (1.5H, br s, unknown), 3.62 (1.5H, s, unknown), 3.93 (0.6H, m, unknown), *4.03* (2H, s, SCH_2), *4.21* (2H, s, SO_2CH_2), *7.20-7.46* (15.7H, br m, ArH of thiosulfonate, CH of chloroform and unknown compounds); δ_C(75 MHz; $CDCl_3$; Me_4Si) 35.4, *40.7*, 56.9, *68.8* (4xCH_2), 126.8, 128.1, 128.3, 128.6, 128.8, 129.2, 130.0 and 131.2 (8xCH); *m/z* (ESI) 301 ([thiosulfonate + Na]$^+$, 30%).

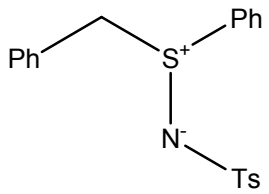
b) White flakes (306 mg, 53%) identified as *N,N'*-diisopropylurea **47** as judged by NMR spectroscopy.

c) White solid (91 mg, crude) identified as the α-disulfone **43** as judged by NMR spectroscopy (when compared with literature data;[207] α-disulfone peaks italicised). δ_H(300 MHz; DMSO; Me_4Si) 0.80-1.28 (7.6H, m, ethanol CH_2 and unknown compounds), 3.70-3.81 (6.2H, m, ethanol CH_3 and unknown compounds), 4.77 (12H, s, unassigned), *5.02* (4H, br s, SO_2CH_2), 6.07 (4H, br s, unassigned, COSY indicates coupling with peak at 5.02 ppm), 7.16-7.40 (53.7H, m, unassigned), *7.43-7.50* (10H, m, ArH of α-disulfone); δ_C(75 MHz; DMSO; Me_4Si; literature ^{13}C NMR data of α-disulfone unavailable) 15.5, 57.8, 61.8, 67.9, 78.9, 79.4, 79.8, 85.2, 126.6, 126.7, 127.3, 127.7, 127.9, 128.2, 128.5, 129.8, 130.6, 125.5, 138.0 and 139.6; *m/z* (ESI) 309 (α-disulfone$^-$ – H, 21%), 293 (α-disulfone$^-$ – OH, 29), 171 (benzylsulfonic acid$^-$ – H, 14).

Benzylsulfinic acid and benzylsulfonic acid could not be identified by ^{13}C NMR spectroscopy. Attempts to repeat the reaction with sodium bicarbonate in place of sodium hydroxide (to minimise hydroxide attack on benzyl chloride) led to a complex mixture of products which could not be compared to literature or the above data.

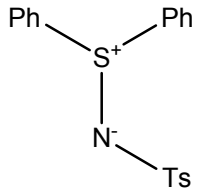
Chapter 4 experimental

S-Benzyl-*S*-phenyl-*N*-tosylsulfimide 44



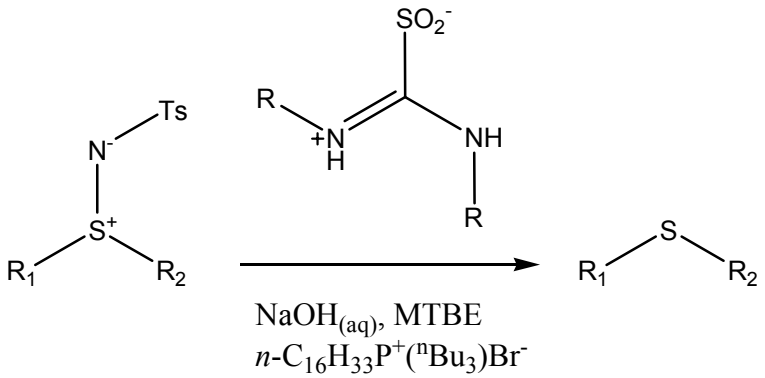
Following a literature procedure,[149] chloramine-T trihydrate (2.92 g, 1.2 equiv.) was added to a solution of *S*-benzyl-*S*-phenylsulfide **46** (1.73 g, 8.64 mmol) in acetonitrile (50 ml) and stirred at RT overnight. The reaction suspension was filtered and the filtrate concentrated *in vacuo* to a pale yellow solid. The crude material was washed with hot water. The resultant white powder was recrystallised from acetone/water to afford white needles (2.51 g, 79%) identified as *S*-benzyl-*S*-phenyl-*N*-tosylsulfimide, in agreement with literature data.[208] 146-148 °C (Found C, 64.88; H, 5.13; N, 3.77. $C_{20}H_{19}NO_2S_2$ requires C, 65.01; H, 5.18; N, 3.79%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.32 (3H, s, CH_3), 4.12 (1H, d, J_{AB} 12.6, CH_2), 4.33 (1H, d, J_{AB} 12.6, CH_2), 6.96 (2H, AA' of AA'BB', *J* 8.1, MeC_6H_4), 7.07 (2H, BB' of AA'BB', *J* 8.1, MeC_6H_4), 7.14-7.23 (2H, m, ArH), 7.25-7.33 (1H, m, ArH), 7.37-7.44 (2H, m, ArH), 7.46-7.55 (3H, m, ArH), 7.60 (2H, d, *J* 8.1, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.4 (CH_3), 60.6 (CH_2), 126.1, 126.7 (2xCH), 127.4 (C_q), 128.8, 129.1, 129.2, 129.5, 130.8, 132.5 (6xCH), 133.6, 141.1 and 141.4 (3xC_q); *m/z* (EI) 369 (M^+, 10%), 279 ($M^+ - CH_2Ph$, 15), 215 ($M^+ - SO_2C_6H_4Me$, 100).

_S,S_-Diphenyl-_N_-tosylsulfimide 45



Following a literature procedure,[149] chloramine-T trihydrate (14.33 g, 1.7 equiv.) was added to solution of *S*,*S*-diphenylsulfide (5 ml, 30 mmol) in acetonitrile (150 ml) and left to stir at RT for 27 h. The white suspension was quenched with dichloromethane and filtered. The filtrate was concentrated *in vacuo* to an off-white solid. Recrystallisation from acetone/water afforded white needles (8.04 g, 75%) identified as *S,S*-diphenyl-*N*-tosylsulfimide, in agreement with literature data.[209] 109-111 °C (Found C, 63.88; H, 4.76; N, 3.89. $C_{19}H_{17}NO_2S_2$ requires C, 64.20; H, 4.82; N, 3.89%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.33 (3H, s, CH_3), 7.13 (2H, AA' of AA'BB', *J* 8.1, $SO_2C_6H_4CH_3$), 7.41-7.52 (6H, m, Ph*H*), 7.60-7.62 (4H, m, Ph*H*), 7.73 (2H, BB' of AA'BB', *J* 8.1, $SO_2C_6H_4CH_3$); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.2 (CH_3), 126.1, 127.0, 128.9, 129.7, 132.1 (5xCH), 136.3, 141.1 and 141.4 ($3xC_q$); *m/z* (EI) 355 (M^+, 100%).

General procedure[83] for the reduction of sulfimides 44 and 45 with thiourea dioxide reducing agents under heterogeneous conditions

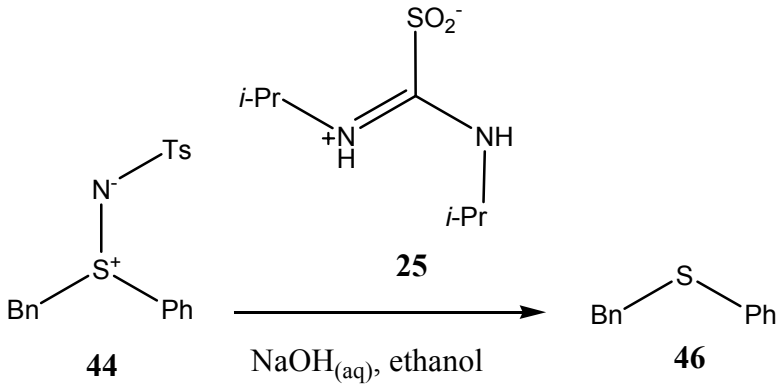


2 M sodium hydroxide (2.7 ml, 3.6 equiv.) was added to a biphasic mixture of the reducing agent (2 equiv.) in water (15 ml), sulfimide (1.5 mmol), *n*-hexadecyltri-*n*-

butylphosphonium bromide (15 mg, 2 mol%), 1,3,5-tri-*tert*-butylbenzene (185 mg, 0.5 equiv., GC internal standard) and methyl *t*-butyl ether (7 ml) and stirred under reflux at 55 ºC for 5 h. A 30 µl aliquot of the reaction mixture was diluted in methyl *t*-butyl ether (1.5 ml) and analysed by GC. The R_t of the GC internal standard is 3.75 min. Conversions for *S*-benzyl-*S*-phenyl-*N*-tosylsulfimide **44** (550 mg, R_t 6.07 min) and *S,S*-diphenyl-*N*-tosylsulfimide **45** (533 mg, R_t 5.20 min) are summarised below.

		GC % conversion	
	Quantity	**44**	**45**
Thiourea dioxide derivative	**/mg**	**R_1 = Bn, R_2 = Ph**	**R_1, R_2 = Ph**
Thiourea dioxide **3**	325	67	59
N,N'-Dicyclohexylthiourea dioxide **17**	817	56	62
N,N'-Diisopropylthiourea dioxide **25**	577	55	49
Propylenethiourea dioxide **26**	445	54	63

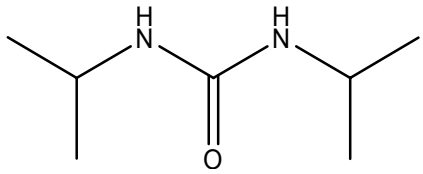
Preparative-scale reduction[83] of *S*-benzyl-*S*-phenyl-*N*-tosylsulfimide 44 with *N,N'*-diisopropylthiourea dioxide 25 in ethanolic sodium hydroxide solution



A suspension of *S*-benzyl-*S*-phenyl-*N*-tosylsulfimide **44** (275 mg, 0.74 mmol), 2 M sodium hydroxide (1.33 ml, 3.6 equiv.), *N,N'*-diisopropylthiourea dioxide **25** (285 mg, 2 equiv.) and ethanol (5 ml) were heated to 50 ºC for 5 h. The reaction was cooled to RT

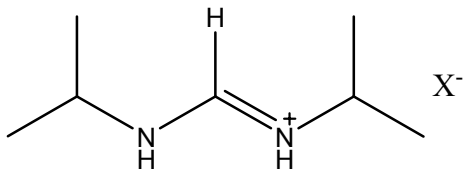
and partitioned over brine and dichloromethane. The layers were separated, the organic layer dried (sodium sulfate), filtered and concentrated *in vacuo* to a white solid. The crude material was purified under flash chromatography (silica, 20 g) using dichloromethane to 7.5% ethanol/dichloromethane to afford a white solid (119 mg, 80%) identified as *S*-benzyl-*S*-phenylsulfide **46**, when compared with an authentic sample. 41-43 °C; δ_H(300 MHz; $CDCl_3$; Me_4Si) 4.15 (2H, s, CH_2), 7.18-7.28 (10H, m, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 38.8 (CH_2), 126.1, 126.9, 128.3, 128.6, 129.6 (5xCH), 136.2 and 137.2 (2xC_q); *m/z* (EI) 200 (M^+, 15%).

***N,N'*-Diisopropylurea 47**



2 M sodium hydroxide (1.33 ml, 1.8 equiv.) was added to a 20 ml scintillation vial containing a suspension of *N,N'*-diisopropylthiourea dioxide **25** (285 mg, 1.48 mmol) in ethanol (5 ml) and heated in an oil bath (oil temperature 55 ºC) for 5 h. The resultant suspension was partitioned over dichloromethane and separated. The organic layer was dried (sodium sulfate) and concentrated *in vacuo* to afford white flakes (200 mg, 94%) identified as the title urea, in agreement with literature data.[210] 194–195 ºC (Found C, 58.23; H, 11.21; N, 19.47, $C_7H_{16}N_2O$ requires C, 58.30; H, 11.18; N, 19.42%); ν_{max}(neat)/cm^{-1} 3336 (NH), 2966 (CH), 1612 (C=O), 1560; δ_H(300 MHz; DMSO; Me_4Si) 1.00 (12H, d, *J* 6.6, CH_3), 3.65 (2H, m, CH), 5.50 (2H, m, NH); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.13 (12H, d, *J* 6.5, CH_3), 3.84 (2H, septuplet, *J* 6.5, CH), 3.90-4.40 (2H, br s, NH); δ_C(75 MHz; DMSO; Me_4Si) 23.6 (CH_3), 41.0 (CH) and 157.2 (C=O); δ_C(75 MHz; $CDCl_3$; Me_4Si) 23.3 (CH_3), 41.9 (CH) and 156.8 (C=O); *m/z* (EI) 144 (M^+, 60%).

Thermal decomposition of *N,N*'-diisopropylthiourea dioxide in ethanol/water

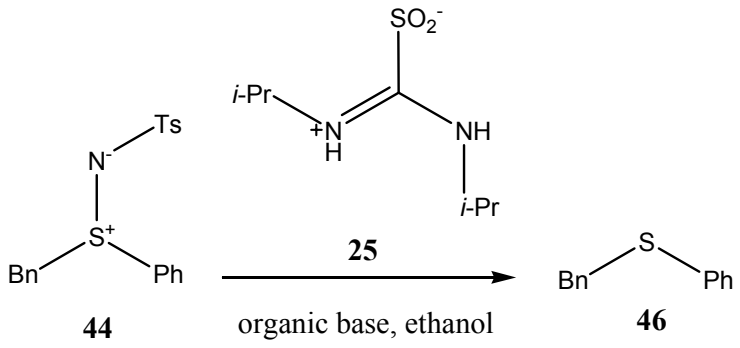


48

A solution of *N,N*'-diisopropylthiourea dioxide **25** (193 mg, 1 mmol) in ethanol (2 ml) and water (3 ml) was heated in a scintillation vial over an oil bath (oil temperature 55 ºC) for 4 h. The pale yellow solution was cooled to RT and concentrated *in vacuo* to a pale yellow oil (248 mg). The NMR spectrum of the crude material in d_1-chloroform was not in agreement with literature data[151] for *N,N*'-diisopropylformamidine and therefore was thought to be the impure salt **48;** the counter-anion is unknown (Found C, 40.25; H, 9.28; N, 13.31; S, 9.52. Formamidinium bisulfate **48** [X = HSO_4] salt $C_7H_{18}N_2O_4S$ requires C, 37.15; H, 8.02; N, 12.37; S, 14.17%); δ_H(300 MHz; DMSO; Me_4Si) 0.90-1.30 (12H, br m, CH_3), 3.45-3.85 (2H, br m, Me_2CH), 7.70-7.90 (1H, br s, CH, non-exchangeable with D_2O); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.28 (12H, d, *J* 6.6, CH_3), 3.56 (2H, m, $CHMe_2$), 7.28 (1H, t, *J* 12.9, amidine CH), 11.27 (2H, br m, NH); δ_C(75 MHz; DMSO; Me_4Si; all peaks listed and unassigned) 21.5, 23.1, 43.9 and 50.3; δ_C(75 MHz; $CDCl_3$; Me_4Si) 23.2 (CH_3), 49.7 and 152.2 (2xCH); *m/z* (ESI) 129 ([formamidine + H]$^+$, 100%).

A repeated experiment to investigate the thermal decomposition of the dioxide **25** in 1,4-dioxane gave the starting dioxide and a trace of *N,N'*-diisopropylurea **47** (weak signals in ^{1}H NMR spectrum, which could not be integrated) after 55 ºC for 5 h.

General procedure[83] for the reduction of *S*-benzyl-*S*-phenyl-*N*-tosylsulfimide 44 with *N,N'*-diisopropylthiourea dioxide 25 in different organic bases



A suspension of *S*-benzyl-*S*-phenyl-*N*-tosylsulfimide **44** (275 mg, 0.74 mmol), organic base (3.6 equiv.), *N,N'*-diisopropylthiourea dioxide **25** (285 mg, 2 equiv.) and solvent (5 ml) were heated to 50 ºC for 5 h. The reaction mixture was cooled to RT and, unless stated otherwise, was concentrated *in vacuo* prior to purification using flash chromatography (silica, 20 g) with 50% petroleum ether 40:60/diethyl ether. *S*-Benzyl-*S*-phenylsulfide **46** and recovered sulfimide were characterised (in comparison with authentic samples) by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry (EI).

a) Triethylamine (0.37 ml, 3.6 equiv.) in ethanol led to the isolation of *S*-benzyl-*S*-phenylsulfide (20 mg, 13%) and unreacted sulfimide (116 mg, 42%).

b) 6-(Di-*n*-butylamino)-1,8-diazobicyclo[5.4.0]undec-7-ene (0.79 ml, 3.6 equiv.) in ethanol gave a crude mixture which was partitioned over saturated ammonium chloride solution and dichloromethane, and separated. The organic layer was concentrated *in vacuo* and purified using flash chromatography as described in the general procedure. The reaction gave *S*-benzyl-*S*-phenylsulfide (26 mg, 18%) and unreacted sulfimide (141 mg, crude, 51%).

c) Pyridine (0.22 ml, 3.6 equiv.) in ethanol gave unreacted sulfimide (273 mg, >99%) only.

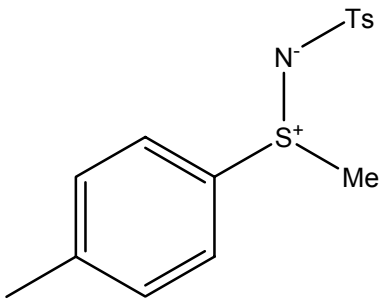
d) 4-*N,N*-Dimethylaminopyridine (325 mg, 3.6 equiv.) in ethanol gave benzylphenyl sulfimide only (9 mg, 6%).

e) 1-*tert*-Butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamino]-2λ^5,4λ^5-catenadi(phosphazene) (P_4-base, 1 M in *n*-hexane, 2.66 ml, 3.6 equiv.) in anhydrous tetrahydrofuran gave a orange-yellow mixture which was partitioned over dichloromethane/saturated ammonium chloride solution and separated. The organic layer was concentrated *in vacuo* and purified using flash chromatography as described in the general procedure. No unreacted sulfimide or benzylphenyl sulfimide could be isolated from any of the fractions. Only *p*-toluenesulfonamide could be isolated (88 mg, 70%).

General procedure[149] for the synthesis of *S*-aryl-*S*-methyl-(*N*-tosyl)-sulfimides

Chloramine-T trihydrate was added to a solution of the sulfide in acetonitrile and stirred overnight at RT. The solution was then quenched with dichloromethane and the solvent removed *in vacuo*. The crude material was then purified using flash chromatography or recrystallisation to give the desired sulfimide.

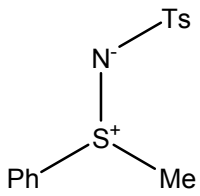
a) ***S*-(*p*-Tolyl)-*S*-methyl-*N*-(*p*-tosyl)sulfimide 50**



p-Methylthioanisole (1.95 ml, 14.47 mmol) was reacted with chloramine-T trihydrate (6.71 g, 1.7 equiv.) in acetonitrile (80 ml) following the general procedure. The crude product mixture was recrystallised in acetone/water to furnish white crystals (1.165 g, 26%) identified as the title compound, in agreement with literature data.[211] 121-122 °C;

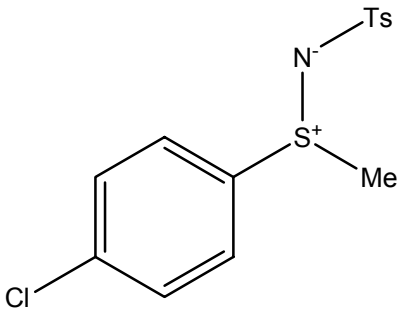
δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.34 (3H, s, $SO_2C_6H_4CH_3$), 2.39 (3H, s, $NSC_6H_4CH_3$), 2.81 (3H, s, SCH_3), 7.16 (2H, AA' of AA'BB', *J* 8.3, ArH), 7.29 (2H, BB' of AA'BB', *J* 8.3, ArH), 7.57 (2H, AA' of AA'BB', *J* 8.3, ArH), 7.73 (2H, BB' of AA'BB', *J* 8.3, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.4, 39.2 (2xCH_3; missing one CH_3), 125.8, 126.3, 129.2, 130.6 (4xCH), 132.6, 141.2, 141.6 and 143.3 (4xC_q); *m/z* (EI) 307 (M^+), 292 (M^+ - Me), 152 (M^+ - $SO_2C_6H_4Me$), 138 (M^+ - $NSO_2C_6H_4Me$).

b) ***S*-Phenyl-*S*-methyl-*N*-(*p*-tosyl)sulfimide 49**



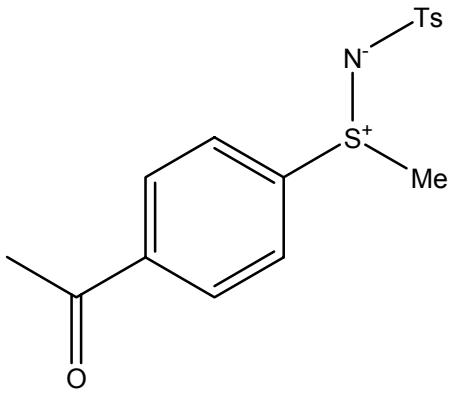
Thioanisole (5 ml, 42.5 mmol) was reacted with chloramine-T trihydrate (32.33 g, 2.7 equiv.) in acetonitrile (150 ml) following the general procedure. The crude solid was purified using flash chromatography with dichloromethane followed by 2.5–15% ethanol/dichloromethane. Recrystallisation from methanol/ethyl acetate furnished a white solid (7.190 g, 58%) identified as the title compound, in agreement with literature data.[212] 128-129 °C; δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.35 (3H, s, $ArCH_3$), 2.84 (3H, s, SCH_3), 7.17 (2H, AA' of AA'BB', *J* 8.2, ArH), 7.51 (3H, m, ArH), 7.70 (2H, m, ArH), 7.74 (2H, BB' of AA'BB', *J* 8.2, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.4, 39.2 (2xCH_3), 125.8, 126.3, 129.2, 130.0, 132.4 (5xCH), 136.1, 141.2 and 141.7 (3xC_q); *m/z* (EI) 293 (M^+), 278 (M^+ - CH_3), 138 (M^+ - $SO_2C_6H_4Me$), 124 (M^+ - $NSO_2C_6H_4Me$).

c) ***S*-(*p*-Chlorophenyl)-*S*-methyl-*N*-(*p*-tosyl)sulfimide 51**



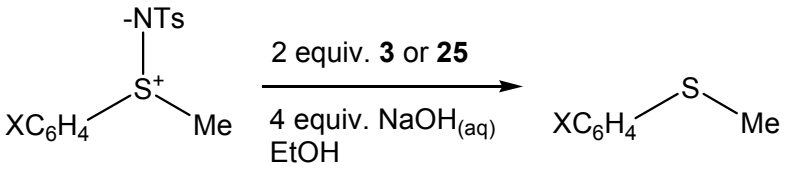
4-Chlorothioanisole (1.9 ml, 13.88 mmol) was reacted with chloramine-T trihydrate (7.00 g, 1.8 equiv.) in acetonitrile (80 ml) following the general procedure. The crude solid was purified using flash chromatography with diethyl ether followed by 2.5-10% methanol/diethyl ether. Recrystallisation from ethyl acetate/petroleum ether (40:60) gave white crystals (1.771 g, 69%) identified as the title compound, in agreement with literature data.[213] 111-112 °C; δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.35 (3H, s, $ArCH_3$), 2.84 (3H, s, SCH_3), 7.17 (2H, AA' of AA'BB', *J* 8.2, ArH), 7.47 (2H, AA' of AA'BB', *J* 8.7, ArH), 7.64 (2H, BB' of AA'BB', *J* 8.7, ArH), 7.72 (2H, BB' of AA'BB', *J* 8.2, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.4, 39.2 (2xCH_3), 126.3, 127.2, 129.3, 130.3 (4xCH) and 139.1 (C_q; missing three C_q); *m/z* (EI) 327 (M^+), 312 (M^+ - CH_3), 172 (M^+ - $SO_2C_6H_4Me$), 158 (M^+ - $NSO_2C_6H_4Me$).

d) ***S*-(*p*-Acetylphenyl)-*S*-methyl-*N*-(*p*-tosyl)sulfimide 52**



4-(Methylthio)acetophenone (0.5 g, 3.00 mmol) was reacted with chloramine-T trihydrate (1.436 g, 1.7 equiv.) in acetonitrile (20 ml). The crude solid was recrystallised from acetone/*n*-pentane to produce pale orange crystals (0.216 g, 22%) identified as the title compound, in agreement with literature data.[213] 174-175 °C; ν_{max}(neat)/cm^{-1} 1681 (C=O); δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.38 (3H, s, $ArCH_3$), 2.56 (3H, s, SCH_3), 2.88 (3H, s, $COCH_3$), 7.20 (2H, AA' of AA'BB', *J* 8.6, ArH), 7.76 (2H, AA' of AA'BB', *J* 8.6, ArH), 7.81 (2H, BB' of AA'BB', *J* 8.6, ArH), 8.08 (2H, BB' of AA'BB', *J* 8.6, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 20.8, 27.0, 37.1 (3xCH_3), 125.7, 126.4, 129.2, 129.3 (4xCH), 139.3, 141.0, 141.3 (3xC_q; missing one C_q) and 197.4 (C=O); *m/z* (EI) 336 (MH^+), 292 (M^+ - CH_3CO), 180 (M^+ - $SO_2C_6H_4Me$).

General procedure[83] for the reduction of *S*-aryl-*S*-methyl-(*N*-tosyl)-sulfimides with thiourea dioxide derivatives under homogeneous conditions



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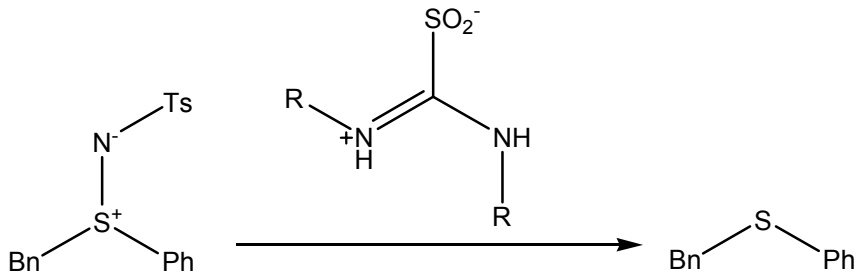
The thiourea dioxide derivative **3** or **25** (2 equiv.) was added to a suspension of *S*-aryl-*S*-methyl-(*N*-tosyl)-sulfimide (0.74 mmol), 2 M sodium hydroxide (1.33 ml, 3.6 equiv.) and

the solvent (5 ml) and heated to 55 ºC in a 20 ml scintillation vial for 5 h. The reactions were monitored by GC under the default program. The quantities of sulfimide used and conversions to sulfide obtained are summarised in below.

X	**Quantity sulfimide used /mg**	**R_t sulfide /min**	**% conversion to sulfide (GC)**	
			3 (160 mg)	**25** (285 mg)
49, H	217	3.00	17	37
50, *p*-Me	227	3.22	39	43
51, *p*-Cl	242	3.50	29	40
52, *p*-Ac	248	4.71	53	67

General procedure[83] for the homogeneous reduction of *S*-benzyl-*S*-phenyl-*N*-tosylsulfimide 44 with thiourea dioxide derivatives – mechanistic studies



The dioxide was added to a suspension of *S*-benzyl-*S*-phenyl-*N*-tosylsulfimide **44** (275 mg, 0.74 mmol), 2 M sodium hydroxide (1.33 ml, 3.6 equiv.) and the solvent (5 ml) and heated to 55 ºC in a 20 ml scintillation vial for 5 h.

a) **Effect of solvent**

The general procedure was followed comparing thiourea dioxide **3** (R = H, 160 mg, 2 equiv.) with *N,N'*-diisopropylthiourea dioxide **25** (R = ^{i}Pr, 285 mg, 2 equiv.). The reactions were carried out in ethanol with the addition of 1,3,5-tri-*tert*-butylbenzene (93

mg, 0.5 equiv.) as the GC internal standard. A 30 μl aliquot of the reaction mixture was diluted in methyl *t*-butyl ether (0.75 ml) and analysed by GC. The R_t of the GC standard is 3.75 min.

	GC % conversion	
Solvent	**3, R = H**	**25, R = ^{i}Pr**
Ethanol	71	>99[b]
Tetrahydrofuran	65	66
1,4-Dioxane	64	66
Acetonitrile	12	28
Benzene	[a]	8
Cyclohexane	[a]	3
Dichloromethane	[a]	7
N,N-Dimethylformamide	[a]	>99

a: Reactions not performed in this solvent; **b**: Reaction repeated with 1 equiv. NaOH (0.68 ml, 2 M) gave 14% conversion by GC.

b) **Effect of sodium hydroxide**

The general procedure was followed using either thiourea dioxide **3** (R = H, 160 mg, 2 equiv.) or *N,N'*-diisopropylthiourea dioxide **25** (R = ^{i}Pr, 285 mg, 2 equiv.), in ethanol (without the use of sodium hydroxide). Following removal of the solvent *in vacuo* both reactions were found to lead to mixtures containing unreacted sulfimide as apparent from ^{1}H and ^{13}C NMR spectroscopic data. No *S*-benzyl-*S*-phenylsulfide was detected when compared with an authentic sample.

c) **Investigation of the reducing species**

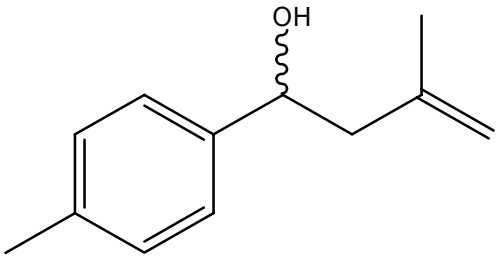
The general procedure was followed using *N,N'*-diisopropylthiourea dioxide **25** (142 mg, 1 equiv.) in ethanol with the addition of 1,3,5-tri-*tert*-butylbenzene (93 mg, 0.5 equiv.) as

the GC internal standard. A 30 μl aliquot of the reaction mixture was diluted in methyl *t*-butyl ether (0.75 ml) and analysed by GC. The R_t of the GC standard is 3.75 min. The reaction resulted in a 44% conversion of sulfimide to sulfide.

d) **Effect of oxygen**

The general procedure was followed using *N,N'*-diisopropylthiourea dioxide **25** (284 mg, 2 equiv.) in degassed ethanol with the addition of 1,3,5-tri-*tert*-butylbenzene (93 mg, 0.5 equiv.) as the GC internal standard under a nitrogen atmosphere. The reaction resulted in a 67% conversion of sulfimide to sulfide.

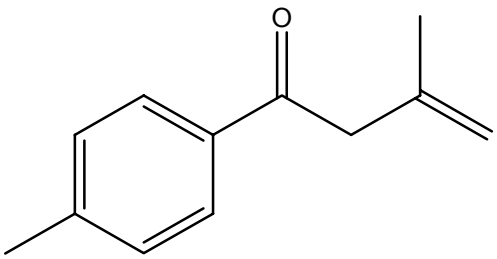
3-Methyl-1-(*p*-tolyl)-3-buten-1-ol 54



Following a literature procedure,[162] *p*-tolualdehyde (1.18 ml, 10 mmol) was added drop wise to a solution of 0.5 M 2-methylallylmagnesium chloride in tetrahydrofuran (30 ml, 1.5 equiv.) which was accompanied by a mild exotherm (RT, increasing to *ca*. 50 ºC). The yellow solution was stirred at RT for 3 h. The solution was decanted onto 300 g crushed ice containing concentrated sulfuric acid (5 ml). The aqueous mixture was extracted with diethyl ether, dried (calcium chloride), filtered and concentrated *in vacuo* to a pale yellow liquid (*ca.* 1.8 g). A Kugelrohr distillation (130 ºC, 5 mbar) afforded a colourless liquid (1.72 g, 98 %) identified as the title compound, in agreement with literature data.[162] ν_{max}(neat)/cm^{-1} 3378 (OH), 3074-2920 (CH), 1647 (C=C), 1046-1019 (C-O); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.80 (3H, s, vinyl-CH_3), 2.08 (1H, s, OH), 2.35 (3H, s, ArCH_3), 2.42 (2H, m, CHCH_2), 4.80 (1H, m, C*H*OH), 4.85 (1H, s, C=CH_2), 4.90 (1H, s, C=CH_2), 7.15 (2H, AA' of AA'BB', *J* 7.8, ArH), 7.25 (2H, BB' of AA'BB', *J* 7.8,

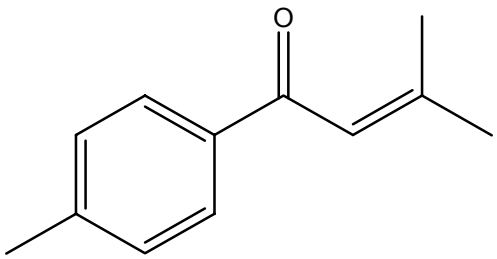
ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.1, 22.4 (2xCH_3), 48.3 (CH_2), 71.3 (CH), 114.0 (CH_2), 125.7, 129.1 (2xCH), 137.2, 141.1 and 142.5 (3xC_q); *m/z* (ESI) 135 (M^- – MeC=CH_2, 100%).

3,4-Dimethyl-3-butenophenone 55



Following a literature procedure,[163] 3-methyl-1-(*p*-tolyl)-3-buten-1-ol **54** (353 mg, 2 mmol) was mixed with pyridinium dichromate (941 mg, 1.25 equiv.) in *N,N*-dimethylformamide (2 ml) and stirred overnight at RT under a nitrogen atmosphere. The resultant suspension was then filtered through a plug of silica and washed with water and diethyl ether. The filtrate was separated, organics dried (sodium sulfate) and concentrated *in vacuo* to a pale yellow oil (340 mg). No purification was carried out and the crude material was taken through to the next isomerisation step. ν_{max}(neat)/cm^{-1} 1677 (C=O).

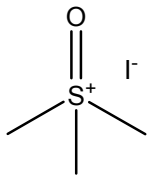
3,4'-Dimethyl-2-butenophenone 56



Following a literature procedure,[162] 3,4-dimethyl-3-butenophenone **55** (340 mg, 1.95 mmol, crude) in ethanol (10 ml) was added to a suspension of sodium ethoxide (136 mg, 1 equiv.) in ethanol (10 ml) and stirred under a nitrogen atmosphere at RT for 15 min.

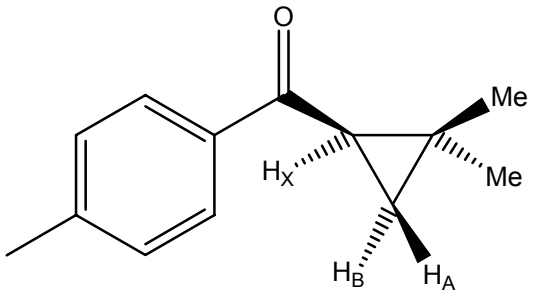
The yellow solution was acidified with glacial acetic acid. Water (40 ml) was then added and the resultant white emulsion was reduced *in vacuo* until only one phase persisted. The aqueous mixture was then partitioned over diethyl ether, separated, organic layer dried (calcium chloride), filtered and concentrated to a yellow oil (*ca.* 280 mg). A Kugelrohr distillation (120 ºC, 5 mbar) furnished a colourless oil (214 mg, 63%) identified as the title compound, in agreement with literature data.[162] ν_{max}(neat)/cm^{-1} 3028-2915 (CH), 1659 and 1606 (C=O); δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.01 (3H, s, CH_3), 2.20 (3H, s, CH_3), 2.40 (3H, s, CH_3), 6.73 (1H, s, CH), 7.24 (2H, AA' of AA'BB', *J* 7.9, ArH), 7.84 (2H, BB' of AA'BB', *J* 7.9, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 20.5, 21.0, 27.3 (3xCH_3), 120.6, 127.7, 128.5 (3xCH), 142.4 and 155.4 (2xC_q); *m/z* (ESI) 174 (M^+, 46%).

_S,S,S_-Trimethylsulfinyl iodide 57



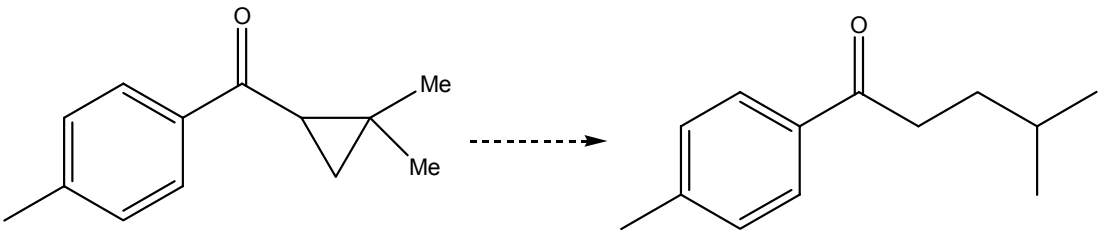
Following a literature procedure,[162] a three-necked flask was charged with dimethylsulfoxide (10.6 ml, 150 mmol) and methyl iodide (22.0 ml, 2.36 equiv.). The reaction was heated to reflux over an oil bath (oil temperature 100 ºC) for 3 d. The mixture was filtered and washed with chloroform. The yellow powder was then recrystallised from water to afford white crystals. The crystals were dried over phosphorus pentoxide in a dessicator and ground to a fine white powder (6.6 g, 20%) identified as the title compound, as judged by elemental analysis. 222-224 ºC (Found C, 16.24; H, 4.12; S, 14.42. C_3H_9IOS requires C, 16.37; H, 4.12; S, 14.57%).

2,2-Dimethyl-1-(*p*-methylbenzoyl)cyclopropane 58



Following a literature procedure,[162] a three-necked flask was charged with *S,S,S*-trimethylsulfinyl iodide **57** (326 mg, 1.2 equiv.) and sodium hydride (59 mg, 1.2 equiv.), then immersed in a water bath and fitted with a calcium chloride drying tube. Dimethylsulfoxide (1 ml, dried over 4A molecular sieves) was added to the flask leading to a white frothy suspension. 3,4'-Dimethyl-2-butenophenone **56** (214 mg, 1.23 mmol) in dimethylsulfoxide (1 ml) was added over 5 min leading to a yellow solution. The reaction was then stirred under a nitrogen atmosphere for 1½ h at RT. The yellow solution was diluted with water, partitioned over diethyl ether, separated, organic layer dried (calcium chloride) and filtered. The filtrate was concentrated and purified using flash chromatography (23 g silica, neutralised with 10% triethylamine/diethyl ether) using *n*-pentane, 10% ethyl acetate/*n*-pentane and then ethyl acetate to afford a yellow oil (185 mg, 80%) identified as 2,2-dimethyl-1-(*p*-methylbenzoyl)cyclopropane, in agreement with literature data[162] (Found C, 82.71; H, 8.64. $C_{13}H_{16}O$ requires C, 82.94; H, 8.57%); ν_{max}(neat)/cm^{-1} 3031-2872 (CH), 1663 (C=O), 1605; δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.93 (1H, dd, J_{AX} 4.1, J_{AB} 7.5, H_A), 1.07 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.50 (1H, dd, J_{AX} 4.1, J_{BX} 5.6, H_X), 2.42 (3H, s, $ArCH_3$), 2.45 (1H, dd, J_{BX} 5.6, J_{AB} 7.5, H_B), 7.26 (2H, AA' of AA'BB', *J* 8.2, ArH), 7.85 (2H, BB' of AA'BB', *J* 8.2, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 18.4, 21.0 (2xCH_3), 26.0 (C_q), 26.4 (CH_2), 32.0, 127.5, 128.5 (3xCH), 135.9, 142.5 (2xC_q) and 197.5 (C=O); *m/z* (EI) 188 (M^+, 55%) and 119 ($MeC_6H_4CO^+$, 100); HRMS (EI) 188.1201, $C_{13}H_{16}O$ requires 188.1207.

Reduction of 2,2-dimethyl-1-(*p*-methylbenzoyl)cyclopropane 58 with thiourea dioxide derivatives



The thiourea dioxide derivative (2 equiv.) was added to a solution of 2,2-dimethyl-1-(*p*-methylbenzoyl)cyclopropane **58** (377 mg, 2 mmol) in 3 M sodium hydroxide (2.7 ml, 4 equiv.) and ethanol (4 ml), fitted with a condenser and heated to 80 ºC for 4 h. The resultant suspension was then filtered. The filtrate was extracted with dichloromethane. The crude filtrate and precipitate were analysed by NMR and were found to contain the starting ketone only. Neither thiourea dioxide (377 mg) nor *N,N'*-diisopropylthiourea dioxide (769 mg) was found to reduce ketone **58**.

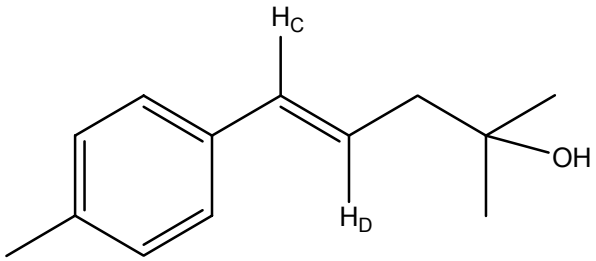
When *N,N'*-diisopropylthiourea dioxide **25** was employed as the reducing agent, the corresponding *N,N'*-diisopropylurea **47** was also found by NMR in the product mixture. The procedure was repeated with higher quantities of reducing agent: *N,N'*-diisopropylthiourea dioxide (10 equiv.) and 3 M sodium hydroxide (20 equiv.) with no change to the result.

Reduction of 2,2-dimethyl-1-(*p*-methylbenzoyl)cyclopropane 58 with sodium borohydride

A solution of 2,2-dimethyl-1-(*p*-methylbenzoyl)cyclopropane **58** (150 mg, 0.8 mmol) in ethanol (2 ml) was added to a solution of sodium borohydride (153 mg, 5 equiv.) in 3 M sodium hydroxide (0.90 ml, 3.4 equiv.) and ethanol (2 ml). The mixture was stirred at RT overnight. The reaction mixture was neutralised with 4 M hydrochloric acid, diluted with brine and extracted with dichloromethane. The organic layer was concentrated to a

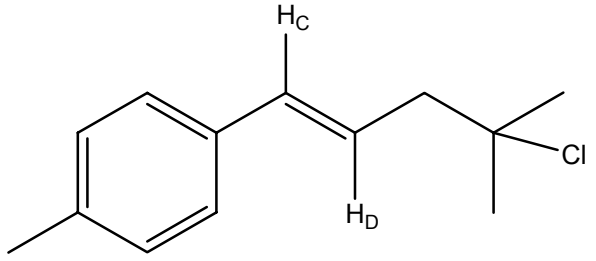
colourless oil and purified using flash chromatography (20 g silica, neutralised with 10% triethylamine/diethyl ether) with *n*-pentane, 5 to 25 % ethyl acetate/*n*-pentane and then 10% ethanol/dichloromethane to furnish two compounds, **60** and **61**. No cyclopropyl alcohol could be isolated and only ring-opened products could be identified.

a) **(*E*)-1-(*p*-Tolyl)-2-(2-hydroxyisobutyl)ethane 60**



Colourless oil (65 mg, 43%). (Found C, 81.75; H, 9.64. $C_{13}H_{18}O$ requires C, 82.06; H, 9.53%); ν_{max}(neat)/cm^{-1} 3356 (OH), 2968-2921 (CH), 1133, 968 (C=O); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.26 (6H, s, CH_3), 1.40 (1H, br s, OH), 2.32 (3H, s, $ArCH_3$), 2.35 (2H, d, *J* 7.5, CH=CH-CH_2), 6.22 (1H, dt, *J* 7.5, J_{CD} 15.6, H_D), 6.41 (1H, d, J_{CD} 15.6, H_C), 7.11 (2H, AA' of AA'BB', *J* 8.1, ArH), 7.27 (2H, BB' of AA'BB', *J* 8.1, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 20.6, 28.6 (2xCH_3), 46.8 (CH_2), 70.3 (C_q), 124.1, 125.4, 128.6, 132.9 (4xCH), 133.9 and 136.4 (2xC_q); *m/z* (ESI) 173 (M^+ - OH, 30%).

b) ***(E)*-1-(*p*-Tolyl)-2-(2-chloroisobutyl)ethane 61**

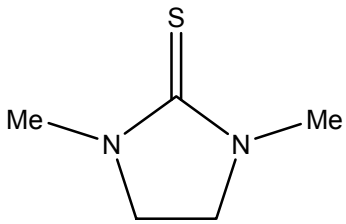


Colourless oil (2 mg, 1.2%). δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.61 (6H, s, CH_3), 2.33 (3H, s, $ArCH_3$), 2.64 (2H, d, *J* 7.1, CH=CH-CH_2), 6.27 (1H, dt, *J* 7.1, J_{CD} 15.6, H_D), 6.43 (1H, d, J_{CD} 15.6, H_C), 7.12 (2H, AA' of AA'BB', *J* 8.1, ArH), 7.28 (2H, BB' of AA'BB', *J* 8.1,

ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 20.6 (CH_3), 29.1 (C_q), 31.6 (CH_3), 48.8 (CH_2), 123.8, 125.5, 128.6, 132.9 (4xCH) 133.5 and 136.6 (2xC_q); *m/z* (ESI) 173 (M^+ - Cl, 25%).

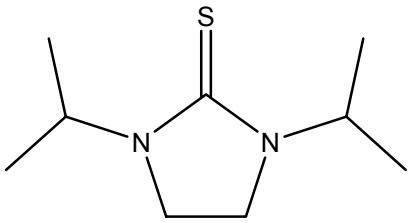
Chapter 5 experimental

N,N'-Dimethylethylenethiourea 62



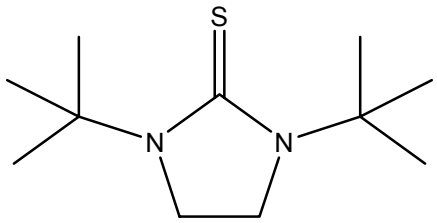
Following a literature procedure,[179] carbon disulfide (2.7 ml, 1 equiv.) was added at the top of condenser over a flask containing *N,N'*-dimethylethylenediamine (4.8 ml, 45 mmol) in pyridine (15 ml). After a mild exotherm (reaction mixture *ca.* 60 ºC) the mixture was heated to reflux over an oil bath (oil temperature 125 ºC) for 2 d. The reaction mixture was cooled to RT, iodine (1.14 g, 0.1 equiv.) added at the top of the condenser and heated to reflux (oil temperature 130 ºC) for 24 h. The reaction was cooled to RT and pyridine removed *in vacuo*. The brown suspension was partitioned over dichloromethane/water, separated, organic layer dried (sodium sulfate), filtered and concentrated to a brown solid. The crude material was recrystallised twice from acetone/petroleum ether (40:60) to give brown crystals (*ca*. 4 g). The crystals were sublimed in a Kugelrohr apparatus (150 ºC, 0.3 mbar) and the resultant pale yellow crystals were recrystallised with acetone/petroleum ether (40:60) to give white crystals (3.71 g, 63%) identified as *N,N'*-dimethylethylenethiourea, in agreement with literature data.[179] 109-110 ºC (Found C, 45.98; H, 7.70; N, 21.48. $C_5H_{10}N_2S$ requires C, 46.12; H, 7.74; N, 21.51%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.14 (6H, s, CH_3), 3.55 (4H, s, CH_2); δ_H(300 MHz; C_6D_6; Me_4Si) 2.35 (6H, s, CH_3), 2.81 (4H, s, CH_2); δ_C(75 MHz; $CDCl_3$; Me_4Si) 35.15 (CH_3), 48.29 (CH_2) and 183.4 (C=S); δ_C(75 MHz; C_6D_6; Me_4Si) 34.8 (CH_3), 46.5 (CH_2) and 184.1 (C=S); *m/z* (EI) 130 (M^+, 100%).

***N,N'*-Diisopropylethylenethiourea 63**



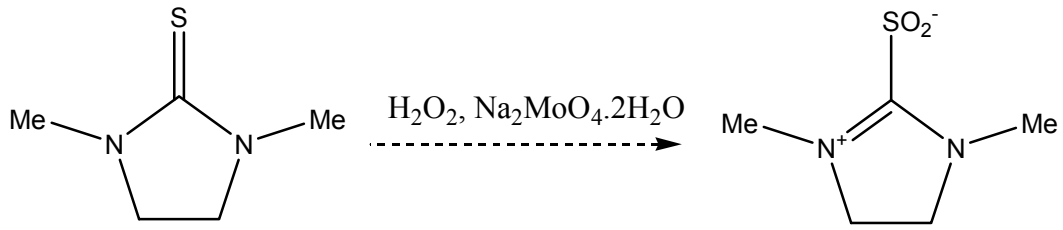
Following a literature procedure,[179] carbon disulfide (5 ml, 1 equiv.) was added at the top of a condenser connected to a flask containing *N,N'*-diisopropylethylenediamine (15 ml, 83 mmol) in pyridine (45 ml). After a mild exotherm (reaction mixture *ca.* 30 ºC) during the addition, the mixture was heated to reflux over an oil bath (oil temperature 130 ºC) for 18 h. The black solution was cooled to RT, iodine (2.11 g, 1 equiv.) added at the top of the condenser and then heated to reflux (oil temperature *ca*. 140 ºC) for 6 d. The reaction was cooled to RT and concentrated *in vacuo* to a black slurry. The crude material was partitioned over dichloromethane/water, separated, organic layer dried (sodium sulfate), filtered and concentrated *in vacuo* to a black solid. Flash chromatography (silica, 25 g) petrol to 50% diethyl ether/petroleum ether (40:60) gave yellow solid which was recrystallised from petroleum ether (40:60) to give off-white needles (9.73 g). The solid was sublimed in a Kugelrohr apparatus (150 ºC, 0.3 mbar) to afford a white powder. Recrystallisation from petroleum ether (40:60) furnished white needles (5.41 g, 35%) identified as *N,N'*-diisopropylethylenethiourea, in agreement with literature data.[179] 87-89 ºC (Found C, 58.13; H, 9.78; N, 15.04. $C_9H_{18}N_2S$ requires C, 58.02; H, 9.74; N, 15.04%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.17 (12H, d, *J* 6.7, CH_3), 3.45 (4H, s, CH_2), 4.92 (2H, septuplet, *J* 6.7, CH); δ_H(300 MHz; C_6D_6; Me_4Si) 0.92 (12H, d, *J* 7.0, CH_3), 2.73 (4H, s, CH_2), 5.15 (2H, septuplet, *J* 7.0, CH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 19.6 (CH_3), 40.5 (CH_2), 46.0 (CH) and 180.7 (C=S); δ_C(75 MHz; C_6D_6; Me_4Si) 19.0 (CH_3), 40.4 (CH_2), 46.9 (CH) and 182.0 (C=S); *m/z* (EI) 186 (M^+, 100%).

***N,N'*-Di-*tert*-butylethylenethiourea 64**



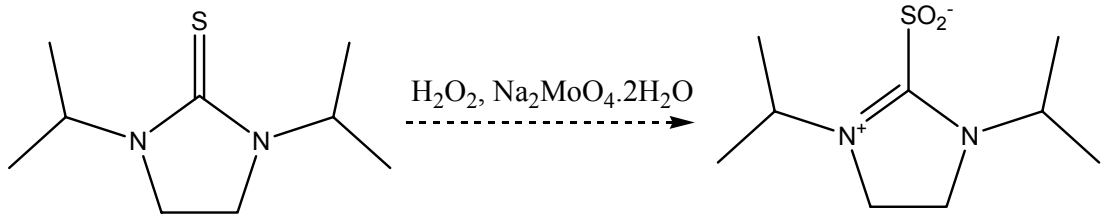
Following a literature procedure,[179] carbon disulfide (3 ml, 1 equiv.) was added at the top of a condenser connected to a flask containing a solution of *N,N'*-di-*tert*-butylethylenediamine (10.76 ml, 50 mmol) in pyridine (15 ml) and heated to reflux over an oil bath (oil temperature 115 ºC) for 5 h. The reaction was cooled to RT, iodine (1.14 g, 0.09 equiv.) added at the top of the condenser and the reaction heated to reflux (oil temperature 130 ºC) for 3 d. The dark brown suspension was cooled to RT and concentrated *in vacuo*. The crude material was partitioned over dichloromethane-water and separated. The organic layer was dried (sodium sulfate), filtered and concentrated to a black oil. The crude material was purified *via* flash chromatography (silica, 20 g, dry-load with dichloromethane) using petroleum ether (40:60) to 50% diethyl ether/petroleum ether (40:60) to afford a orange powder (385 mg, 4%) identified as *N,N'*-di-*tert*-butylethylenethiourea, in agreement with literature data.[179] 129-131 ºC; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.60 (18H, s, CMe_3), 3.45 (4H, s, CH_2); δ_H(300 MHz; C_6D_6; Me_4Si) 1.54 (18H, s, CMe_3), 2.74 (4H, s, CH_2); δ_C(75 MHz; $CDCl_3$; Me_4Si) 28.11 (CH_3), 44.49 (CH_2), 56.70 (C_q) and 183.61 (C=S); δ_C(75 MHz; C_6D_6; Me_4Si) 28.1 (CH_3), 44.0 (CH_2), 56.4 (C_q) and 184.1 (C=S); *m/z* (EI) 214 (M^+, 70%).

Sodium molybdate catalysed oxidation of *N,N'*-dimethylethylenethiourea 62 with hydrogen peroxide



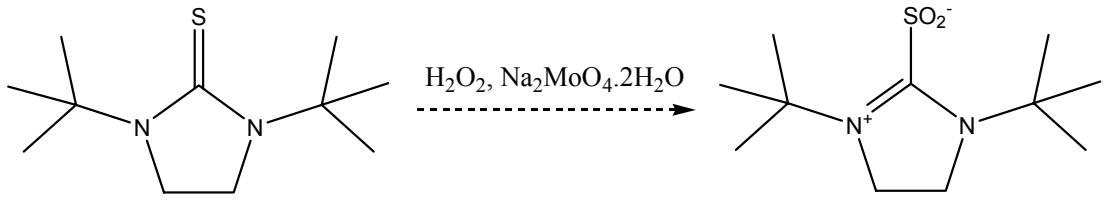
Following a literature procedure,[58] 30% hydrogen peroxide (0.23 ml, 2 equiv.) was added to cooled solution (-10 ºC) of *N,N'*-dimethylethylenethiourea **62** (130 mg, 1 mmol), sodium molybdate dihydrate (2 mg, 1 mol%), diethyl ether (3 ml) and 1,4-dioxane (2 ml) and stirred at -10 ºC under a nitrogen atmosphere for 3 h. Starting material was still present as shown by TLC (R_f thiourea 0.3, UV and I_2; baseline: unknown spot, UV; diethyl ether). The solvent was removed under a stream of nitrogen at RT to give an off-white gum which was found to comprise of a mixture of products including starting thiourea and an unknown compound thought to be a *N,N'*-dimethylimidazolinium salt (15:1, deduced from ^{1}H NMR spectroscopy). Only imidazolinium salt peaks are listed. ν_{max}(neat)/cm^{-1} 1663 (C=N); δ_H(300 MHz; DMSO; Me_4Si) 3.07 (6H, s, CH_3), 3.85 (4H, s, CH_2), 8.39 (1H, s, CH, HMQC NMR reveals ^{1}H-^{13}C coupling with ^{13}C signal at 158.4 ppm); δ_C(75 MHz; DMSO; Me_4Si) 34.1 (CH_3), 50.3 (CH_2) and 158.4 (CH).

Sodium molybdate catalysed oxidation of *N,N'*-diisopropylethylenethiourea 63 with hydrogen peroxide



Following a literature procedure,[58] 30% hydrogen peroxide (0.12 ml, 2 equiv.) was added to cooled solution (-10 ºC) of *N,N'*-diisopropylethylenethiourea **63** (93 mg, 0.5 mmol), sodium molybdate dihydrate (1 mg, 1 mol%), diethyl ether (3 ml) and 1,4-dioxane (2 ml) and stirred at -10 ºC under a nitrogen atmosphere for 3 h. Starting material was still present as shown by TLC (R_f thiourea **63** is 0.3, UV and I_2; baseline: unknown spot, UV; diethyl ether). The solvent was removed under a stream of nitrogen at RT to give a buff gum. The crude material was found to comprise of an unknown compound thought to be the corresponding imidazolinium salt. ν_{max}(neat)/cm^{-1} 2973 (CH), 1642 (C=N); δ_H(300 MHz; DMSO; Me_4Si) 1.25 (12H, d, *J* 6.6, CH_3), 3.79-3.91 (6H, m, CH and CH_2), 8.45 (1H, s, CH, HMQC NMR experiment reveals coupling with ^{13}C 154.9 ppm); δ_C(75 MHz; DMSO; Me_4Si) 20.2 (CH_3), 44.7 (CH_2), 49.4 and 154.9 (2xCH).

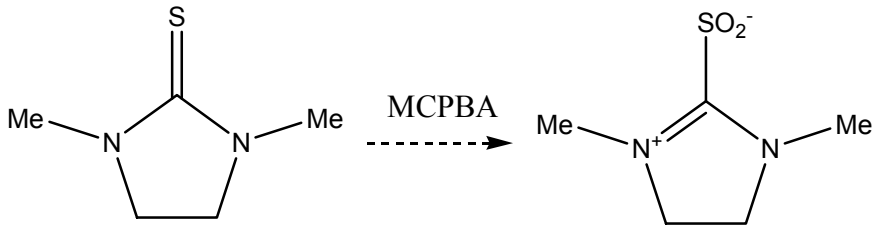
Sodium molybdate catalysed oxidation of *N,N'*-di-*tert*-butylethylenethiourea 64 with hydrogen peroxide



Following a literature procedure,[58] 30% hydrogen peroxide (0.20 ml, 2 equiv.) was added to cooled solution (-10 ºC) of *N,N'*-di-*tert*-butylethylenethiourea **64** (190 mg, 0.89 mmol), sodium molybdate dihydrate (1.8 mg, 1 mol%), diethyl ether (5 ml) and 1,4-dioxane (5

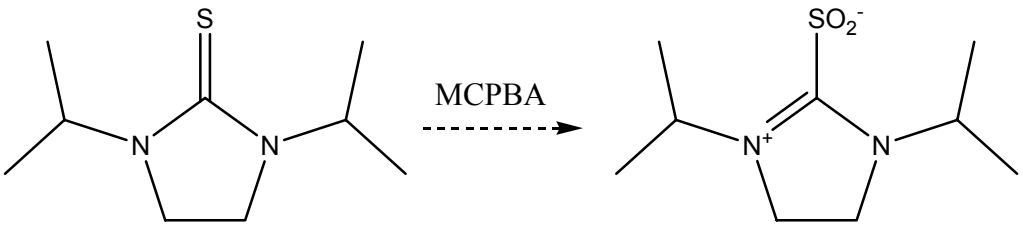
ml) and stirred at -10 ºC under a nitrogen atmosphere for 6 h. Starting material was still present as shown by TLC (R_f thiourea 0.7, UV and I_2; R_f unknown spot 0.4, I_2 only; diethyl ether). 30% hydrogen peroxide (0.20 ml, 2 equiv.) was added, maintaining the temperature at -10 ºC and stirred for 1 h. The resultant solution was brought to RT and concentrated under a stream of nitrogen at RT. The addition of tetrahydrofuran failed to furnish crystals of the dioxide.[47] The reaction was then concentrated *in vacuo* to give a brown oil. The crude product could not be identified by ^{1}H NMR spectroscopy (in d_6-benzene) when compared with authentic samples and literature data. Starting thiourea (50 mg, 26%) was recovered from the reaction.

***meta*-Chloroperbenzoic acid oxidation of *N,N'*-dimethylethylenethiourea 62**



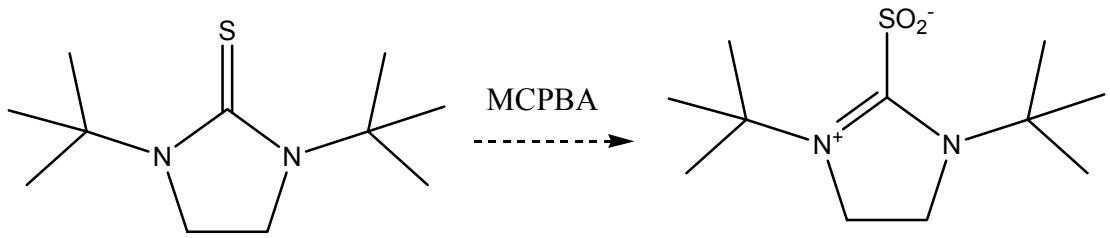
meta-Chloroperbenzoic acid (345 mg, 2 equiv.) was added to a cooled solution of the *N,N'*-dimethylethylenethiourea **62** (130 mg, 1 mmol) in tetrahydrofuran (10 ml, -10 ºC) and then brought to RT and stirred under a nitrogen atmosphere for 3 h. The resultant colourless solution was reduced under a stream of nitrogen at RT to furnish a white crystalline powder. Spectroscopic analysis revealed that the crude material comprised of starting thiourea, *m*-chlorobenzoic acid and an unknown product thought to be a *N,N'*-dimethylimidazolinium salt (1:0.5:1.3, as deduced by ^{1}H NMR spectroscopy). IR and ^{1}H NMR spectroscopic analyses were in agreement with data obtained from the hydrogen peroxide/molybdate mediated oxidation. ^{13}C NMR spectroscopic data differed at the amidinium CH; all peaks are listed. δ_C(75 MHz; DMSO; Me_4Si) 34.1 (CH_3), 50.3 (CH_2) and 166.0 (CH, couples to ^{1}H at 8.37 ppm).

meta-Chloroperbenzoic acid oxidation of *N,N'*-diisopropylethylenethiourea 63



meta-Chloroperbenzoic acid (172 mg, 2 equiv.) was added to a cooled solution of the *N,N'*-diisopropylethylenethiourea **63** (93 mg, 0.5 mmol) in tetrahydrofuran (5 ml) cooled to -10 ºC. The reaction was brought to RT and stirred under a nitrogen atmosphere for 3 h. The resultant white emulsion was reduced under a stream of nitrogen at RT to give buff solid. Spectroscopic analysis revealed that the crude material comprised of starting thiourea, *m*-chlorobenzoic acid and an unknown product thought to be a *N,N'*-diisopropylimidazolinium salt (1:0.2:0.5, ^{1}H NMR). IR and NMR spectroscopic analyses of the imidazolinium salt were in agreement with data obtained from hydrogen peroxide/molybdate mediated oxidation.

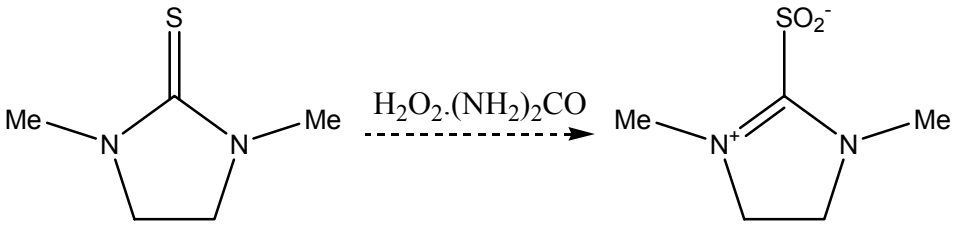
meta-Chloroperbenzoic acid oxidation of *N,N'*-di-*tert*-butylethylenethiourea 64



meta-Chloroperbenzoic acid (161 mg, 2 equiv.) was added to a cooled solution of the *N,N'*-di-*tert*-butylethylenethiourea **64** (100 mg, 0.47 mmol) in tetrahydrofuran (10 ml, -10 ºC) and then brought to RT and stirred under a nitrogen atmosphere for 3 h. TLC showed complete consumption of thiourea. The white suspension was filtered and washed with diethyl ether to yield a white powder (40 mg) which was not identified as the required dioxide. The identity of the product was most likely impure thiourea trioxide

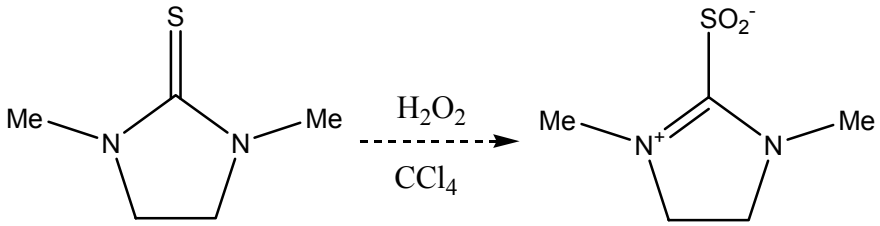
monohydrate or impure imidazolinium bisulfate salt, as shown by elemental and NMR spectroscopic analyses (Found C, 45.43; H, 8.30; N, 9.90; S, 10.97. *N,N'*-Di-*tert*-butylimidazolinium bisulfate $C_{11}H_{24}N_2O_4S$ requires C, 47.12; H, 8.63; N, 9.99; S, 11.44%); ν_{max}(neat)/cm^{-1} 1625 (C=N), 1159, 1060; δ_H(300 MHz; DMSO; Me_4Si) 1.35 (18H, s, CH_3), 3.91 (4H, s, CH_2), 8.08 (1H, s, CH, non-exchangeable with D_2O; HMQC NMR experiment reveals coupling with ^{13}C 152.8 ppm); δ_C(75 MHz; DMSO; Me_4Si) 27.3 (CH_3), 44.7 (CH_2), 56.0 (C_q) and 152.8 (CH); *m/z* (LSIMS) 183 (M^+ - SO_2, 100%).

Oxidation of *N,N'*-dimethylethylenethiourea 62 with urea hydrogen peroxide



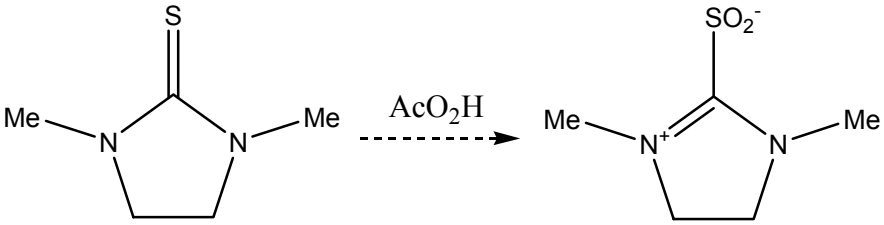
Urea hydrogen peroxide (188 mg, 2 equiv.) was added to a solution of *N,N'*-dimethylethylenethiourea **62** (130 mg, 1 mmol) and bis(acetylacetonato)dioxomolybdenum(VI) (3 mg, 1 mol%) cooled to -5 ºC in tetrahydrofuran (5 ml), over 3A molecular sieves, and stirred for 3 h under a nitrogen atmosphere. The resultant buff gum was filtered and washed with diethyl ether. The crude gum was thought to be the corresponding imidazolinium salt, as judged by ^1H and ^{13}C NMR spectroscopy. The NMR spectra were identical to the NMR spectra obtained for the molybdate/hydrogen peroxide mediated oxidation.

Non-catalytic oxidation of *N,N'*-dimethylethylenethiourea 62 with hydrogen peroxide



Following a literature procedure,[28] 30% hydrogen peroxide (0.17 ml, 3 equiv.) was added to an ice-cooled suspension of *N,N'*-dimethylethylenethiourea **62** (65 mg, 0.5 mmol) in carbon tetrachloride (2 ml). The mixture was stirred under a nitrogen atmosphere for RT at 3 h. An aliquot of the carbon tetrachloride layer was taken from the biphasic mixture and analysed by TLC, ^{1}H and ^{13}C NMR spectroscopy, at ½ h and at 3 h reaction times. Both analyses revealed only starting thiourea in the sample.

Peracetic acid oxidation of *N,N'*-dimethylethylenethiourea 62



Peracetic acid (32 µl, 32% w/w, 2 equiv.) was added to a solution of *N,N'*-dimethylethylenethiourea **62** (10 mg, 0.077 mmol) in benzene (1 ml) and sonicated for 30 min. The biphasic layer was separated. The aqueous layer was concentrated *in vacuo* (45 ºC, 16 mbar) to a colourless oil and found to contain a *N,N'*-dimethylimidazolinium salt. NMR spectroscopic data was identical to mixture obtained for the hydrogen peroxide/molybdate mediated oxidation.

General procedure for the oxidation of *N,N'*-dimethylethylenethiourea 62 with inorganic oxidising agents

A 20 ml scintillation vial was charged with *N,N'*-dimethylethylenethiourea **62** (65 mg, 0.5 mmol), dichloromethane (10 ml) and oxidant (2 equiv.) and capped. The contents were stirred at room temperature for 4 d. The crude product was filtered through a plug of celite and washed with dichloromethane. The filtrate was concentrated and analysed crude.

a) Tetra-*n*-propylammonium perruthenate (18 mg, 10 mol%) and *N*-methylmorpholine-*N*-oxide (117 mg, 2 equiv.) were employed as the oxidant following the general procedure. The crude brown liquid was found to contain a complex mixture of starting material, *N*-methylmorpholine (when compared with an authentic sample) and a trace of *N,N'*-dimethylimidazolidin-2-one **67** by NMR (in d_1-chloroform).

b) *N*-Methylmorpholine-*N*-oxide (117 mg, 2 equiv.) was employed as the oxidant following the general procedure. The white solid was found to contain starting material and other unidentifiable products by NMR (in d_1-chloroform).

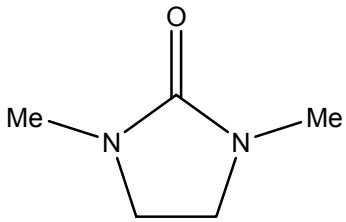
c) A ground mixture[180] of potassium permanganate (158 mg, 2 equiv.) and manganese(IV) dioxide (953 mg, 11 equiv.) was employed as the oxidant following the general procedure. The colourless liquid was found to contain a complex mixture of products, where only *N,N'*-dimethylimidazolidin-2-one **67** and starting material could be identified by NMR spectroscopy (in d_1-chloroform).

General procedure for the formation of *N,N'*-disubstituted imidazolidin-2-ones from disubstituted ethylenethioureas

30% hydrogen peroxide (1.23 ml, 6 equiv.) was added to a 20 ml scintillation vial charged with the thiourea (2 mmol), bis(acetylacetonato)dioxomolybdenum(VI) (1 mg, 0.1 mol%), 2 M sodium hydroxide (2 ml, 2 equiv.) and ethanol (10 ml), capped and

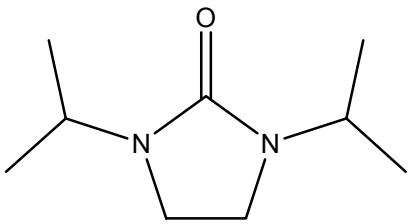
stirred at RT for 72 h. The reaction mixture was neutralised with 3 M hydrochloric acid, partitioned over dichloromethane and separated. The organic layer was dried (magnesium sulfate), filtered and concentrated to a colourless oil. The crude mixture was purified under flash chromatography (silica, 25 g) to give the target urea.

a) ***N,N*'-Dimethylimidazolidin-2-one 67**



N,N'-Dimethylethylenethiourea **62** (261 mg, 2 mmol) was converted to the corresponding urea by following the general procedure. Flash chromatography using 50% diethyl ether/petroleum ether (40:60) to 10% methanol/diethyl ether gave a colourless liquid (44 mg, 19%) identified as the title compound, impure by elemental analysis (Found C, 48.12; H, 9.07; N, 22.22. $C_5H_{10}N_2O$ requires C, 52.61; H, 8.83; N, 24.54%); ν_{max}(neat)/cm^{-1} 1679 (C=O); δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.80 (6H, s, CH_3), 3.31 (4H, s, CH_2); δ_H(300 MHz; C_6D_6; Me_4Si) 2.40 (2H, s, CH_2), 2.51 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$; Me_4Si) 31.5 (CH_3), 45.1 (CH_2) and 162.1 (C=O); δ_C(75 MHz; C_6D_6; Me_4Si) 30.8 (CH_3), 44.1 (CH_2) and 161.0 (C=O); *m/z* (LSIMS) 115 (MH^+, 10%).

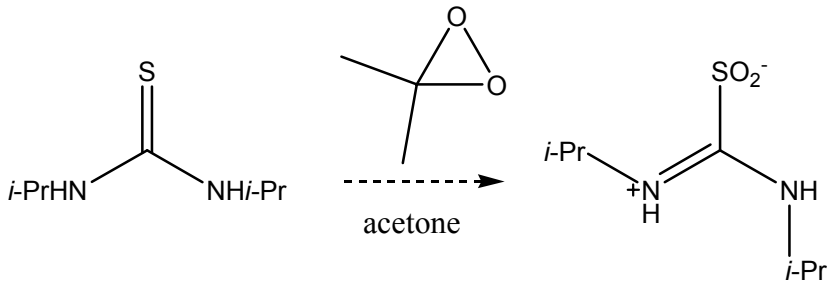
b) ***N,N*'-Diisopropylimidazolidin-2-one 68**



N,N'-Diisopropylethylenethiourea **63** (373 mg, 2 mmol) was converted to the corresponding urea by following the general procedure. Flash chromatography using

10% diethyl ether/petroleum ether (40:60) to diethyl ether gave a colourless liquid (55 mg, 16%) identified as *N,N*'-diisopropylimidazolidin-2-one, impure by elemental analysis (Found C, 60.25; H, 10.61; N, 15.47. $C_9H_{18}N_2O$ requires C, 63.49; H, 10.66; N, 16.45%); ν_{max}(neat)/cm^{-1} 1675 (C=O); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.09 (12H, d, *J* 6.8, CH_3), 3.21 (4H, s, CH_2), 4.13 (2H, septuplet, *J* 6.8, CH); δ_H(300 MHz; C_6D_6; Me_4Si) 0.88 (12H, d, *J* 6.7, CH_3), 2.61 (4H, s, CH_2), 4.30 (2H, septuplet, *J* 6.7, CH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 19.5 (CH_3), 37.2 (CH_2), 43.4 (CH) and 164.0 (C=O); δ_C(75 MHz; C_6D_6; Me_4Si) 19.4 (CH_3), 37.3 (CH_2), 43.6 (CH) and 160.1 (C=O); *m/z* (LSIMS) 171 (MH^+, 100%).

Reaction of *N,N'*-diisopropylthiourea with dioxirane derivatives 69 and 70

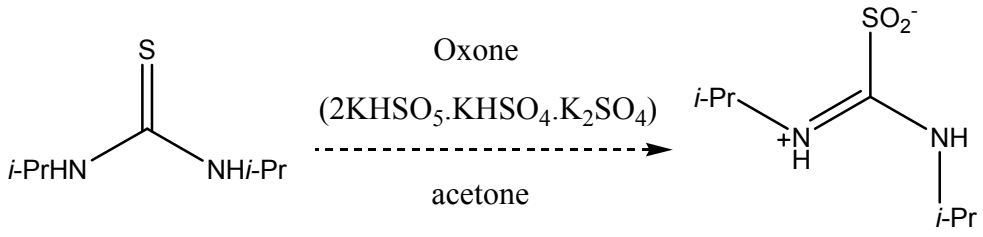


Following a literature procedure,[182] oxone (25 g, 41 mmol) was added *via* a powder addition flask to a suspension of acetone (13 ml, 177 mmol), sodium bicarbonate (12 g, 143 mmol) and water (20 ml) in a three-necked flask. The dimethyldioxirane vapour **69** was directed through an air condenser and glass gas inlet tube into a two-necked flask containing a solution of *N,N'*-diisopropylthiourea (80 mg, 0.5 mmol) in acetone (5 ml). The two-necked flask was also connected to a scrubber containing saturated potassium iodide (50 ml). A yellow colouration of the potassium iodide solution occurs and no anticipated precipitation of *N,N*'-diisopropylthiourea dioxide in acetone occurred during the addition of oxone to acetone for the first 10 min. Peroxides were detected qualitatively with iodine-starch strips and with sodium iodide/acetone/acetic acid solution in the thiourea solution flask. A stream of nitrogen was bubbled through the thiourea solution flask to remove volatile peroxides and the thiourea solution flask was brought to

RT. A trace of white solid began to precipitate out of solution once the flask was at RT. The solvent was evaporated under a stream of nitrogen at RT and the resultant white solid analysed by TLC and ^{1}H NMR spectroscopy. Both analyses revealed the presence of *N,N'*-diisopropylurea **47**. The potassium iodide scrubber was titrated against 0.001 N sodium thiosulfate and found to contain 1 mmol (2 equiv.) of oxidising vapour, presumably dimethyldioxirane.

The reaction was repeated with 1,1,1-trifluoroacetone (60 equiv.) in place of acetone as a reactant, thus generating methyl(trifluoromethyl)dioxirane **70**, in place of dimethyldioxirane **69**. 1,1,1-Trifluoroacetone has an atmospheric boiling point of 22 ºC. Therefore, all syringes and reaction flasks were cooled prior to contact with 1,1,1-trifluoroacetone. The reaction of dioxirane **70** with *N,N'*-diisopropylthiourea yielded no improvement towards synthesising the dioxide **25**. TLC and NMR spectroscopic data indicated a complex mixture of compounds of which only the starting thiourea could be identified. Titration of the potassium iodide scrubber revealed that 2.5 equiv. of an oxidising vapour, presumably methyl(trifluoromethyl)dioxirane, had bypassed the thiourea solution.

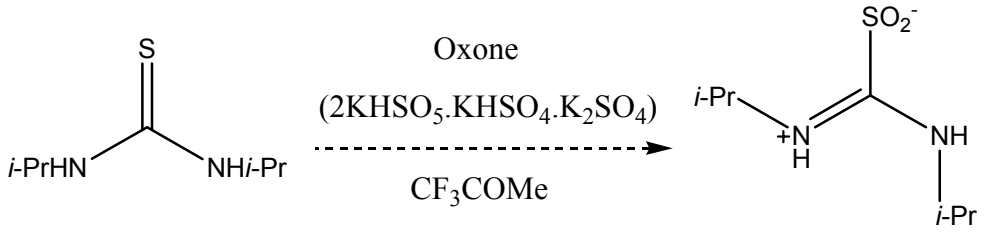
Oxidation of *N,N'*-diisopropylthiourea with oxone in acetone



A flask (attached to a potassium iodide scrubber) was charged with *N,N'*-diisopropylthiourea (160 mg, 1 mmol), oxone (1.23 g, 2 equiv.) and acetone (10 ml) and stirred under a nitrogen atmosphere at RT for 7 h. The resultant buff suspension was filtered, washed with petroleum ether (40:60), acetone and diethyl ether. The filtrate was concentrated under a stream of nitrogen at RT. The filtrate gave a complex NMR

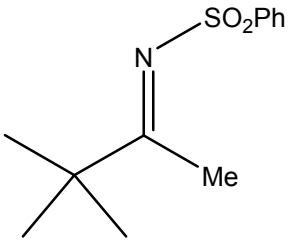
spectrum in which only *N,N'*-diisopropylurea **47** could be identified. The precipitate could not be identified by NMR spectroscopy.

Oxidation of *N,N'*-diisopropylthiourea with oxone in 1,1,1-trifluoroacetone



Oxone (1.23 g, 2 equiv.) was added to a solution of *N,N'*-diisopropylthiourea (160 mg, 1 mmol), dichloromethane (10 ml) and 1,1,1-trifluoroacetone (0.45 ml, 5 equiv.) cooled in an ice-salt bath. No apparent frothing or bumping occurred. The reaction was stirred at 0 °C for 4 h under a nitrogen atmosphere. Neither the colouration of the scrubber nor the formation of the dioxide by TLC, was apparent. The flask was brought to RT at which point the scrubber began to bubble and turn yellow in colour. The reaction mixture was stirred at RT overnight. The resultant yellow suspension was found to contain no starting material by TLC and was filtered and washed with chloroform. The precipitate could not be identified. The filtrate was concentrated *in vacuo* to a yellow solid to give a complex NMR spectrum in which only *N,N'*-diisopropylurea **47** could be identified.

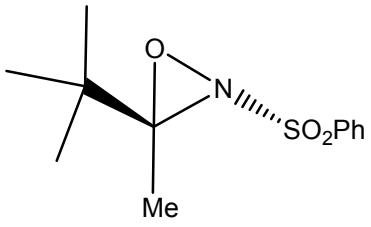
***N*-(1,2,2-Trimethylpropylidene)benzenesulfonamide 71**



Following a literature procedure,[189] a solution of titanium(IV) chloride (5.5 ml, 1 equiv.) in anhydrous dichloromethane (50 ml) was added drop wise over 1 h to a suspension of pinacolone (6.25 ml, 50 mmol), benzenesulfonamide (7.86 g, 1 equiv.) and 1,1,2-

trichloroethane (250 ml) cooled to 0 °C. The resultant orange-brown suspension was brought to RT and heated to reflux over an oil bath (oil temperature 100 °C) under a nitrogen atmosphere overnight. The resultant brown suspension was filtered through a celite pad and washed with dichloromethane. The yellow-brown filtrate was concentrated *in vacuo* to a brown oil. The oil was partitioned over dichloromethane and 5% potassium carbonate solution, and separated. The organic layer was washed with water, dried (magnesium sulfate), filtered and concentrated to a yellow-brown oil (14.8 g, 50 mmol). TLC and ^{1}H NMR spectroscopic data were in agreement with literature data[189] and the crude imine was used in the next step without further purification. R_f 0.20 (10% ethyl acetate/petroleum ether 40:60); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.17 (9H, s, CMe_3), 2.57 (3H, s, CH_3), 7.49-7.63 (3H, m, ArH), 7.96-8.02 (2H, m, ArH); δ_H(300 MHz; C_6D_6; Me_4Si) 0.75 (9H, s, CMe_3), 2.33 (3H, s, CH_3), 6.90-6.95 (3H, m, ArH), 8.07-8.11 (2H, m, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 19.8, 27.2 (2xCH_3), 43.2 (C_q), 126.8, 128.7, 132.5 (3xCH), 141.7 and 195.8 (2xC_q); δ_C(75 MHz; C_6D_6; Me_4Si) 19.9, 26.8 (2xCH_3), 42.7 (C_q; missing one aromatic-C_q), 127.2, 128.8, 132.2 (3xCH), C=N not observed.

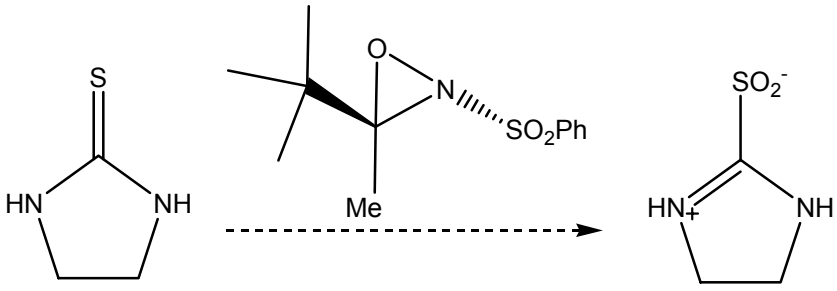
***trans*-3-(1,1-Dimethylethyl)-3-methyl-2-(phenylsulfonyl)oxaziridine 72**



Following a literature procedure,[189] *meta*-chloroperbenzoic acid (13.5 g, 77% grade, 1.2 equiv.) was added to a biphasic mixture of *N*-(1,2,2-trimethylpropylidene)benzenesulfonamide **71** (14.8 g, crude, 50 mmol) in saturated potassium carbonate (300 ml) and dichloromethane (200 ml). No exotherm was observed. The reaction mixture was stirred under a nitrogen atmosphere for 3 h. The resultant yellow suspension was poured onto water (1 l) and separated. The aqueous

layer was extracted with dichloromethane (300 ml). All organic layers were combined, washed with sodium bicarbonate followed by water, and then dried (magnesium sulfate) and filtered. The yellow solution was concentrated *in vacuo* to a brown oil. A low temperature recrystallisation (ice-salt bath temperature) from petroleum ether (40:60) furnished a yellow solid (8 g, 63%) identified as *trans*-3-(1,1-dimethylethyl)-3-methyl-2-(phenylsulfonyl)oxaziridine, in agreement with literature data.[189] 183-184 °C (Found C, 56.33; H, 6.71; N, 5.58; S, 12.50. $C_{12}H_{17}NO_3S$ requires C, 56.45; H, 6.71; N, 5.49; S, 12.56%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.96 (9H, s, CMe_3), 2.05 (3H, s, CH_3), 7.54-7.70 (3H, m, ArH), 7.97-8.03 (2H, m, ArH); δ_H(300 MHz; C_6D_6; Me_4Si) 0.76 (9H, s, CMe_3), 1.97 (3H, s, CH_3), 6.76-6.87 (3H, m, ArH), 7.93-7.98 (2H, m, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 13.7, 25.0 (2xCH_3), 37.2, 93.0 (2xC_q), 128.1, 129.1, 134.0 (3xCH) and 138.6 (C_q); δ_C(75 MHz; C_6D_6; Me_4Si) 13.5, 24.3 (2xCH_3), 36.5, 92.4 (2xC_q), 127.6, 128.5, 133.1 (3xCH) and 138.8 (C_q); The oxaziridine was found to decompose in d_6-dimethylsulfoxide after 6 h on standing at RT in the light, to the imine precursor, *N*-(1,2,2-trimethylpropylidene)benzenesulfonamide **71**; *m/z* (ESI) 279 (MNa^+, 21%), 253 (M^+ - H, 50).

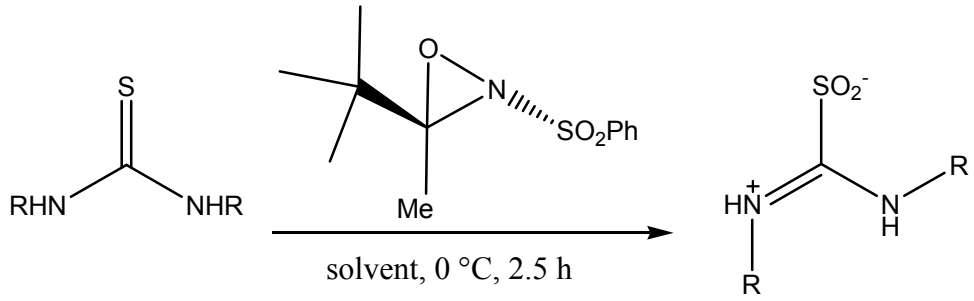
Reaction of *trans*-3-(1,1-dimethylethyl)-3-methyl-2-(phenylsulfonyl)oxaziridine 72 with ethylenethiourea 5



A solution of *trans*-3-(1,1-dimethylethyl)-3-methyl-2-(phenylsulfonyl)oxaziridine **72** (510 mg, 5 equiv.) in a carbon tetrachloride (2 ml) was added to a Schlenk tube charged with a suspension of the ethylenethiourea **5** (41 mg, 0.4 mmol) in a carbon tetrachloride

(3 ml) cooled over an ice-salt bath. On complete addition, the reaction was brought to RT and stirred for 2½ h under a nitrogen atmosphere. The suspensions were filtered and washed with carbon tetrachloride to furnish a buff crystalline powder (35 mg). The buff crystalline powder tested positive for dithionite ions. NMR spectroscopic analysis revealed the presence of a mixture of mostly starting thiourea **5**, the corresponding dioxide **6** and 2-imidazoline **7**. ν_{max}(neat)/cm^{-1} 1077 (ν_{as} SO_2), 1028, 1007 (ν_s SO_2); δ_H(300 MHz; D_2O; 1,4-dioxane) 3.70 (4H, s, CH_2 thiourea), 3.93 (0.3H, s, CH_2 2-imidazoline), 4.00 (0.5H, s, CH_2 dioxide).

General procedure for the oxidation of thiourea derivatives with *trans*-3-(1,1-dimethylethyl)-3-methyl-2-(phenylsulfonyl)oxaziridine 72



A solution of *trans*-3-(1,1-dimethylethyl)-3-methyl-2-(phenylsulfonyl)oxaziridine **72** (510 mg, 2 equiv.) in an organic solvent was added to a Schlenk tube charged with a suspension of the thiourea (1 mmol) in a solvent cooled over an ice-salt bath. On complete addition, the reaction was brought to RT and stirred for 2½ h under a nitrogen atmosphere. The suspensions were filtered and washed with diethyl ether. The filtrate was found to contain the corresponding imine **71**.

a) ***N,N'*-Dicyclohexylthiourea dioxide 17**

A solution of the oxaziridine **72** (255 mg, 2 equiv.), in diethyl ether (4 ml) and 1,4-dioxane (2 ml), was reacted with *N,N'*-dicyclohexylthiourea (120 mg, 0.5 mmol) in diethyl ether (2 ml) and 1,4-dioxane (2 ml) following the general procedure. The

resultant white powder (130 mg, 96%) was identified as *N,N'*-dicyclohexylthiourea dioxide **17**, impure by elemental analysis. NMR spectroscopic analysis could not be carried out because of the poor solubility of the product in NMR solvents. IR spectroscopic data was identical to data obtained with the hydrogen peroxide mediated oxidation of *N,N'*-dicyclohexylthiourea. Found C, 56.46; H, 9.00; N, 10.08; S, 11.55. $C_{13}H_{24}N_2O_2S$ requires C, 57.32; H, 8.88; N, 10.28; S, 11.77%.

b) ***N,N'*-Diphenylthiourea dioxide 19**

Attempts to isolate *N,N'*-diphenylthiourea dioxide using tetrahydrofuran or 3:2 diethyl ether/1,4-dioxane as solvents following the general procedure were unsuccessful. Precipitation did not occur therefore the imine could not be separated from the other products. Consequently, the reaction mixture was reduced under a stream of nitrogen at RT. The reaction was found to be completed as evident from the complete conversion of oxaziridine to imine, as deduced from the ^{1}H NMR spectrum. The ^{1}H and ^{13}C NMR spectra of the crude foam were too complex to interpret.

c) ***N,N'*-Di-*tert*-butylthiourea dioxide 20**

Attempts to isolate dioxide **20** *via* oxidation of *N,N'*-di-*tert*-butylthiourea with oxaziridine **72** failed. A solution of the oxaziridine **72** (255 mg, 2 equiv.), in diethyl ether (4 ml) and 1,4-dioxane (2 ml), was reacted with *N,N'*-di-*tert*-butylthiourea (94 mg, 0.5 mmol) in diethyl ether (2 ml) and 1,4-dioxane (2 ml) following the general procedure. The resultant white powder (30 mg, 38%) was thought to correspond to the formamidinium salt. IR and NMR spectroscopic data were identical to the data of the formamidinium salt formed from the hydrogen peroxide mediated oxidation of *N,N'*-di-*tert*-butylthiourea. Found C, 42.74; H, 8.55; N, 10.86. *N,N'*-Di-*tert*-butylformamidinium bisulfate $C_9H_{22}N_2O_4S$ requires C, 42.50; H, 8.72; N, 11.01%.

d) ***trans*-4,5-Tetramethyleneimidazolidin-2-sulfinic acid 23**

Attempts to isolate dioxide **23** *via* oxidation of *trans*-4,5-tetramethyleneimidazolidin-2-thione **22** with oxaziridine **72** failed. Oxaziridine **72**, dissolved in carbon tetrachloride (2 ml), was added to *trans*-4,5-tetramethyleneimidazolidin-2-thione **22** (156 mg, 1 mmol) in carbon tetrachloride (8 ml) following the general procedure. The resultant yellow solid (120 mg) tested positive for dithionite ions. ν_{max}(neat)/cm^{-1} 1086 (ν_{as} SO_2) and 1010 (ν_s SO_2); The oxaziridine **72** mediated oxidation of *trans*-4,5-tetramethyleneimidazolidin-2-thione was found to have no improvement over the non-catalytic hydrogen peroxide in carbon tetrachloride conditions. The ^{1}H NMR spectrum (in d_6-dimethylsulfoxide) was too complex to interpret. Some NMR signals were indicative of the imine and, presumably, the dioxide (when compared with the data obtained from the hydrogen peroxide/carbon tetrachloride conditions). Suspected dioxide **23** ^{13}C NMR peaks are italicised; δ_C(75 MHz; DMSO; Me_4Si) *23.5*, *28.1*, 28.7 (3xCH_2), 62.2, 63.7, 64.0, *65.1* and 160.2 (5xCH).

e) ***N,N'*-Diisopropylthiourea dioxide 25**

Oxaziridine **72,** dissolved in tetrahydrofuran (2 ml), was added to *N,N'*-diisopropylthiourea (160 mg, 1 mmol) in tetrahydrofuran (8 ml) following the general procedure. The resultant white powder (160 mg, 83%) was identified as *N,N'*-diisopropylthiourea dioxide **25**, and tested positive for dithionite ions. Mpt, IR and NMR spectroscopic (in d_1-chloroform) and MS data of the product were in agreement with the data obtained from the hydrogen peroxide/molybdate oxidation conditions. Found C, 43.71; H, 8.71; N, 14.80; S, 14.03. $C_7H_{16}N_2O_2S$ requires C, 43.73; H, 8.39; N, 14.57; S, 16.68%.

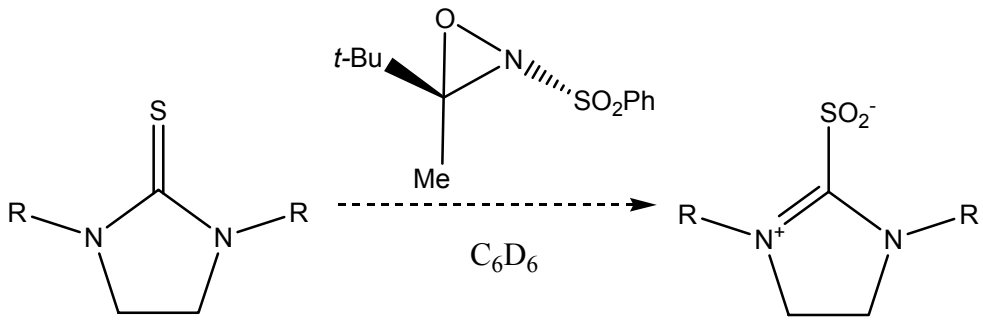
f) **Propylenethiourea dioxide 26**

Oxaziridine **72,** dissolved in tetrahydrofuran (2 ml), was added to propylenethiourea (116 mg, 1 mmol) in tetrahydrofuran (8 ml) following the general procedure. The resultant white powder (120 mg, 81%) was identified as propylenethiourea dioxide, which tested positive for dithionite ions. Mpt, IR and NMR spectroscopic (in deuterium oxide) and MS data of the product were in agreement with the data obtained from the hydrogen peroxide/molybdate oxidation conditions. Additional NMR spectroscopic data in d_6-dimethylsulfoxide, obtained from the oxaziridine **72** mediated oxidation, are provided (Found C, 32.68; H, 5.43; N, 19.21; S, 21.96. $C_4H_8N_2O_2S$ requires C, 32.42; H, 5.44; N, 18.90; S, 21.64%); δ_H(300 MHz; DMSO; Me_4Si) 1.78 (2H, quintuplet, *J* 5.6, CH_2), 3.29 (4H, t, *J* 5.6, CH_2), 9.14 (2H, br s, NH); δ_C(75 MHz; DMSO; Me_4Si) 18.1, 38.2 (2xCH_2) and 174.2 (CS).

g) ***N,N'*-Dimesitylthiourea dioxide 31**

Oxaziridine **72,** dissolved in 3:2 diethyl ether/1,4-dioxane (2 ml), was added to *N,N'*-dimesitylthiourea (312 mg, 1 mmol) in 3:2 diethyl ether/1,4-dioxane (8 ml) following the general procedure. The resultant white powder (276 mg, 80%) was identified as *N,N'*-dimesitylthiourea dioxide **31**. Mpt, IR and NMR spectroscopic (in d_6-dimethylsulfoxide) and MS data of the product were in agreement with the data obtained from the hydrogen peroxide/molybdate oxidation conditions. Residual 1,4-dioxane was found in the product, as deduced by NMR spectroscopy, similar to the observation using hydrogen peroxide/molybdate conditions. Gentle heating under vacuum (45 ºC, 0.3 mbar) in an attempt to evaporate the solvent was unsuccessful and hence the product was impure (Found C, 66.49; H, 7.36; N, 7.90; S, 6.05. $C_{19}H_{24}N_2O_2S$ requires C, 66.25; H, 7.02; N, 8.13; S, 9.31%); HRMS (LSIMS) found 367.1451, $C_{19}H_{24}N_2O_2S$+Na requires 367.1456.

General procedure for the reaction of *N,N*'-disubstituted ethylenethioureas with *trans*-3-(1,1-dimethylethyl)-3-methyl-2-(phenylsulfonyl)oxaziridine 72: NMR studies



The thiourea (0.077 mmol) was dissolved in d_6-benzene (0.35 ml) and analysed by proton NMR to confirm structure under current conditions. *trans*-3-(1,1-Dimethylethyl)-3-methyl-2-(phenylsulfonyl)oxaziridine **72** (2 equiv.) in d_6-benzene (0.35 ml) was then mixed with the thiourea sample and sonicated at RT for 45 min.

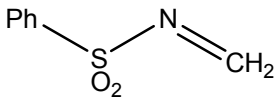
a) *N,N'*-Dimethylethylenethiourea **62** (5 mg, 0.038 mmol) and *trans*-3-(1,1-dimethylethyl)-3-methyl-2-(phenylsulfonyl)oxaziridine **72** (19 mg, 2 equiv.) were used following the general procedure. The oxaziridine was thought to be consumed as evident from the identification of the respective imine **71** in the ^{1}H NMR spectrum. The integrals were difficult to analyse and only peaks in the 0-3 ppm range are listed. Suspected carbene signals (compared with literature[173] data) are italicised. δ_H(300 MHz; C_6D_6; Me_4Si) 0.75 (s, imine CH_3), 0.88, 1.55, 1.73 (each preceding signal is a singlet), 2.33 (s, thiourea CH_2), 2.36 (s, imine CH_3), *2.42*, 2.53 (each preceding signal is a singlet), *2.81* (s, thiourea/carbene CH_3). The reaction was repeated at 40 ºC but resulted in no change to the reaction, as shown from the NMR spectroscopic analysis.

b) *N,N'*-Diisopropylethylenethiourea **63** (5 mg, 0.027 mmol) and *trans*-3-(1,1-dimethylethyl)-3-methyl-2-(phenylsulfonyl)oxaziridine **72** (14 mg, 2 equiv.) were used following the general procedure. The NMR study revealed the presence of starting thiourea and imine **71** but no corresponding carbene **85** (when compared with

literature[173] data). When the reaction was repeated at higher temperature, no change to the ^{1}H NMR spectrum was observed.

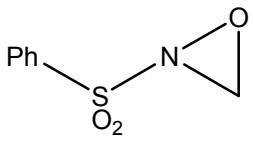
c) *N,N'*-Di-*tert*-butylethylenethiourea **64** (5 mg, 0.023 mmol) and *trans*-3-(1,1-dimethylethyl)-3-methyl-2-(phenylsulfonyl)oxaziridine **72** (12 mg, 2 equiv.) were used following the general procedure. The NMR study revealed the presence of starting thiourea and imine **71** only. The reaction at higher temperature was not repeated.

Phenylsulfonimine 73



Following a literature procedure,[191] formaldehyde diethylacetal (1.25 ml, 1 equiv.) was added to a flask charged with benzenesulfonamide (1.57 g, 10 mmol) and connected to a short fractionating column and short-path condenser. The mixture was heated to reflux over an oil bath (oil temperature 100 ºC) over 2 d. The buff suspension cooled to RT and filtered. The product was insoluble in d_1-chloroform. NMR spectroscopic analysis in d_6-dimethylsulfoxide revealed only starting sulfonamide.

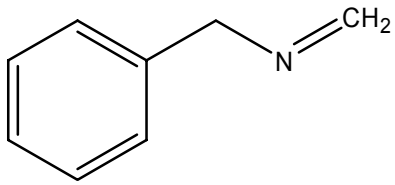
***N*-Phenylsulfonyloxaziridine 74**



Peracetic acid (0.84 ml, 32% w/w, 2 equiv.) was added to a solution of benzenesulfonamide (314 mg, 2 mmol) and formaldehyde diethylacetal (0.5 ml, 2 equiv.) in methanol (5 ml) cooled over an ice-bath. The reaction was stirred under a nitrogen atmosphere for 4 h at RT. Volatile solvents were evaporated *in vacuo* (RT, 16 mbar). The resultant white suspension was partitioned over dichloromethane and water and

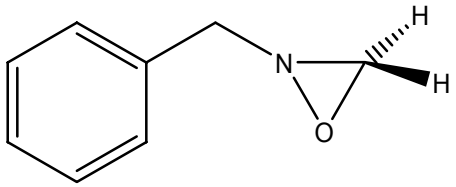
separated. The organic layer was washed with saturated sodium carbonate solution, dried (magnesium sulfate), filtered and concentrated *in vacuo* to a crystalline white solid (200 mg) identified as the starting sulfonamide by NMR spectroscopic analysis.

_N_-Methylenebenzylamine 75



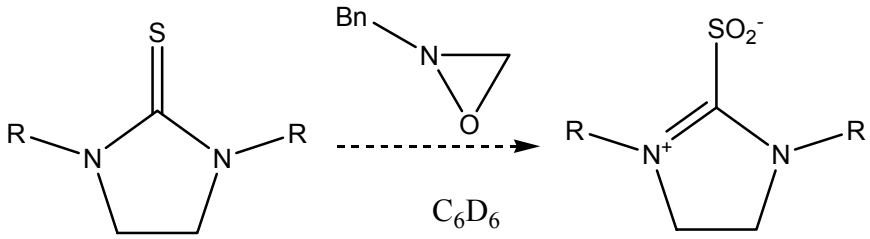
Following a literature procedure,[198] formaldehyde solution (8.6 ml, 37% w/w in water, 2.9 equiv.) was added to a solution of benzylamine (10.9 ml, 100 mmol) in ethanol (50 ml) cooled to 0 °C. The resultant white emulsion was heated to reflux over an oil bath (oil temperature 105 °C) for 3 days. The colourless emulsion was cooled to RT and reduced *in vacuo* to give a colourless oil. The oil was partitioned over water and dichloromethane, and separated. The organic layer was dried (magnesium sulfate), filtered and concentrated to a colourless oil which was identified as the required imine, in agreement with literature data[198] (10.1 g, 85%). ν_{max}(neat)/cm^{-1} 3084-2771, 1493, 1452; δ_H(400 MHz; $CDCl_3$; Me_4Si) 3.45 (2H, br s, N=CH_2), 3.70 (2H, s, PhCH_2), 7.20-7.40 (5H, m, Ph); δ_H(400 MHz; C_6D_6; Me_4Si) 3.32 (2H, br s, N=CH_2), 3.51 (2H, s, PhCH_2), 7.05-7.32 (5H, m, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 57.0, 73.8 (2xCH_2), 127.0, 128.2, 128.9 (3xCH) and 138.4 (C_q); δ_C(75 MHz; C_6D_6; Me_4Si) 57.2, 74.1 (2xCH_2), 127.2 (CH), 128.3 (C_q), 128.5 and 129.1 (2xCH); *m/z* (LSIMS) 120 (MH^+, 33%).

_N_-Benzyloxaziridine 76



Peracetic acid (0.5 ml, 32% w/w, 1.2 equiv.) was added to a solution of *N*-methylenebenzylamine **75** (240 mg, 2 mmol) in dichloromethane (10 ml) cooled over an ice-bath. The resultant solution was stirred for 30 min at RT at which time all of the imine **75** was consumed as shown by TLC. The solution was partitioned over water and separated. The organic layer was washed with saturated sodium carbonate, dried (magnesium sulfate) and concentrated to remove most of the solvent to afford *ca.* 2 ml of a colourless dichloromethane solution. The oxaziridine was found to decompose within minutes if heated above 35 °C or if handled neat. Attempts to distil the crude product at reduced pressure also lead to breakdown. The dichloromethane solutions tested positive for peroxides with sodium iodide/acetic acid/acetone (*ca.* 5 mg/2 drops/5 ml quantities, respectively) and were found to breakdown after *ca.* 3 days at RT (as judged by ^{1}H NMR spectroscopy). NMR spectroscopic analysis of the product revealed a complex mixture of compounds and only diagnostic peaks are listed. All assignments were verified with COSY and HMQC NMR experiments. δ_H(300 MHz; C_6D_6; Me_4Si) 2.96 (1H, d, *J* 10.3, OCH_2), 3.24 (1H, d, *J* 13.5, PhCH_2), 3.43 (1H, d, *J* 10.3, OCH_2), 3.44 (1H, d, *J* 13.5, PhCH_2), 6.97-7.44 (>5H, br m, complex ArH); δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.78 (1H, d, *J* 10.2, OCH_2), 3.84 (2H, s, PhCH_2), 4.05 (1H, d, *J* 10.2, OCH_2), 7.27-7.58 (5H, m, ArH); δ_C(75 MHz; C_6D_6; Me_4Si) 66.4 (PhCH_2), 70.8 (OCH_2) and 127.2-149.7 (multiple aryl-C signals, complex); δ_C(75 MHz; $CDCl_3$; Me_4Si) 66.4 (PhCH_2), 71.5 (OCH_2N) and 127.0-150.2 (multiple aryl-C signals, complex).

General procedure for the reaction of *N,N*'-disubstituted ethylenethioureas with *N*-benzyloxaziridine 76: NMR studies



The thiourea (0.077 mmol) was dissolved in d_6-benzene (0.5 ml) and analysed by proton NMR spectroscopy. *N*-Benzyloxaziridine **76** (crude dichloromethane solution) in d_6-benzene was then mixed with the thiourea sample and sonicated at RT for 30 min. Proton, carbon and HMQC NMR spectroscopic analyses were performed to monitor the reaction. All thioureas gave complex NMR spectra with no sign of *N*-benzylmethyleneamine **75**, anticipated as a by-product from the reduction of the *N*-benzyloxaziridine. Residual oxaziridine was detected; however, the remaining products could not be identified. Wide-range (0-500 ppm) carbon NMR experiments failed to reveal carbenic centres (when compared with literature[173] data). The major proton singlet peaks are listed. Assignment of the peaks in the NMR spectra could not be confidently carried out.

a) *N,N'*-Dimethylethylenethiourea **62** (10 mg, 0.077 mmol) was reacted with *N*-benzyloxaziridine **76** (*ca.* 35 mg, 2 equiv.) following the general procedure and the thiourea was found to be consumed after 30 min. The NMR spectroscopic data was inconclusive. δ_H(300 MHz; C_6D_6; Me_4Si) 2.43 (1H, s, couples to ^{13}C at 44.7 and 47.6 ppm), 2.51 (0.4H, s, couples to ^{13}C at 31.3 ppm), 2.82 (1.1H, s, couples to ^{13}C at 34.8 ppm), 4.36 (0.6H, s, couples to ^{13}C at 53.4 ppm) and 5.00 (0.3H, s, couples to ^{13}C at 62.6).

b) *N,N'*-Dimethylethylenethiourea **62** (10 mg, 0.077 mmol) was reacted with *N*-benzyloxaziridine **76** (*ca.* 52 mg, 5 equiv.) following the general procedure and the thiourea was found to be consumed after 30 min. The NMR spectroscopic data was inconclusive. δ_H(300 MHz; C_6D_6; Me_4Si) 2.42 (1H, s, couples with ^{13}C at 43.3 ppm), 2.45 (0.5H, s, couples with ^{13}C at 46.2 ppm), 2.48 (1.7H, s, couples with ^{13}C at 33.5 ppm), 2.80 (0.6H, s), 4.40 (4.2H, s, couples with ^{13}C at 52.1 ppm), 4.99 (0.6H, s, couples with ^{13}C at 56.5 ppm). The NMR solvent was evaporated at RT under a stream of nitrogen, to give a yellow-brown oil which tested negative for dithionite ions. The crude mixture was heated over an oil bath (oil temperature 80 °C) for 3 h to promote elimination of sulfur dioxide or sulfur trioxide. The brown oil was analysed again by ^1H NMR spectroscopy and GCMS but contained products which could not be identified confidently. δ_H(300 MHz; C_6D_6; Me_4Si) 2.36 (1H, s), 2.37 (0.6H, s), 2.47 (1.6H, s) and 2.79 (0.9H, s); GCMS (CI, CH_4) [MH^+, R_t, GC %abs] 115 (*N,N'*-dimethylimidazolidin-2-one **67**, 5.3 min, 50), 122 (*N*-benzylmethyleneamine **75**, 5.8 min, 100), 131 (*N,N'*-dimethylethylenethiourea **62**, 7.0 min, 60), 164 (*N,N'*-dimethylethylenethiourea dioxide **65**, 8.3 min, 25).

c) *N,N'*-Dimethylethylenethiourea **62** (10 mg, 0.077 mmol) was reacted with *N*-benzyloxaziridine **76** (*ca.* 104 mg, 10 equiv.) following the general procedure. The thiourea was found to be consumed after 30 min. Excess oxaziridine was found by NMR spectroscopy. The NMR spectroscopic data was inconclusive. δ_H(300 MHz; C_6D_6; Me_4Si) 2.47 (1H, s, couples with ^{13}C at 43.3 ppm), 2.50 (1.5H, s, couples to ^{13}C at 30.0 ppm), 4.46 (6H, s, couples with ^{13}C at 52.2 ppm), 5.02 (1H, couples s, with ^{13}C at 64.5 ppm). The NMR solvent was evaporated at RT to give a yellow-brown oil and tested negative for dithionite ions. The crude mixture was heated over an oil bath (oil temperature 80 °C) for 3 h to promote elimination of sulfur dioxide or sulfur trioxide. The brown oil was analysed again by NMR and GCMS but contained products which could not be identified confidently. δ_H(300 MHz; C_6D_6; Me_4Si) 2.36

(1H, s) and 2.45 (1.9H, s); GCMS, CI, CH_4 (MH^+, R_t, GC abs%) 115 (*N,N'*-dimethylimidazolidin-2-one **67**, 5.3 min, 30), 122 (*N*-benzylmethyleneamine **75**, 5.8 min, 100), 134 (*N*-benzyloxaziridine **76**, 7.0 and 7.2 min, 25), 164 (*N,N'*-dimethylethylenethiourea dioxide **67**, 8.3 min, 10).

d) *N,N'*-Diisopropylethylenethiourea **63** (14 mg, 0.077 mmol) was reacted with *N*-benzyloxaziridine **76** (*ca.* 35 mg, 2 equiv.) following the general procedure. The thiourea was found to remain unreacted after 30 min and 4½ h, as deduced from the NMR spectra.

e) *N,N'*-Diisopropylethylenethiourea **63** (14 mg, 0.077 mmol) was reacted with *N*-benzyloxaziridine **76** (*ca.* 162 mg, 15.6 equiv.) following the general procedure. The thiourea was found to remain unreacted after 1 h, where only starting thiourea and oxaziridine were identified in the ^{1}H NMR spectrum. Heating the NMR tube contents over a water bath (water temperature 33 ºC) for 4 h resulted in no change. Further heating to 60 ºC for 4 h gave a complex NMR spectrum, in which oxaziridine **76** was not detected.

Reaction of *N,N*'-dimethylethylenethiourea 65 with *N*-benzyloxaziridine 76: preparative scale, work-up investigations

N-Benzyloxaziridine **76** (*ca.* 1.35 g in 3 ml dichloromethane, 10 equiv.) was added to a solution of *N,N*'-dimethylethylenethiourea **62** (130 mg, 1 mmol) in benzene (1 ml) and stirred at RT for 1 h. A mild exotherm (RT to *ca.* 40 °C) occurred when the starting materials were mixed, leading to the formation of a white suspension followed by a yellow solution. The volatile solvents were removed under a stream of nitrogen at RT. The resultant brown oil was triturated with methyl *t*-butyl ether and sonicated for 15 min to give a pale yellow gum in a yellow supernatant. The methyl *t*-butyl ether layer was separated from the gum and evaporated under a stream of nitrogen at RT. Proton and carbon NMR spectroscopic analyses of the gum were indicative of aromatic containing

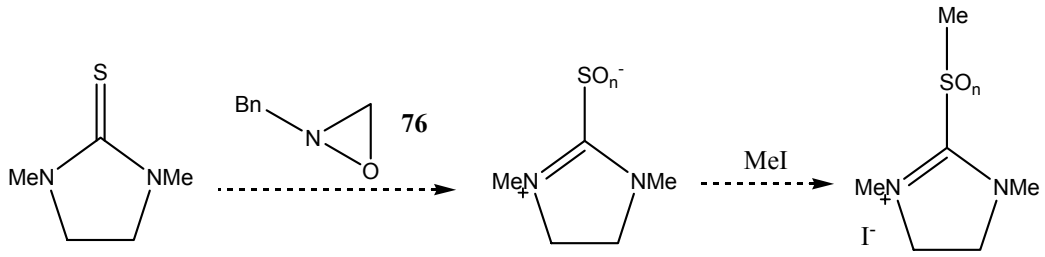
residues, too complex to interpret. The proton and carbon NMR spectra of the methyl *t*-butyl ether extract were indicative of a complex mixture of products, in which *N,N'*-dimethylimidazolidin-2-one **67** was identified.

The experiment was repeated twice, as above, with acidic work-up (2 M HCl) and basic work-up (saturated sodium carbonate) procedures. Both experiment conditions gave brown oils, identified as crude mixtures containing *N,N'*-dimethylimidazolidin-2-one **67**.

Attempts to oxidise *N,N*'-diisopropylethylenethiourea **63** and *N,N*'-di-*tert*-butylethylenethiourea **64** with oxaziridine **76** failed. In both experiments, the respective thioureas were detected in the crude reaction mixture, as judged by NMR spectroscopy.

An attempt to oxidise *N,N'*-diisopropylthiourea with oxaziridine **76** gave unknown products too complex to identify using NMR spectroscopy.

Reaction of *N,N*'-dimethylethylenethiourea 62 with *N*-benzyloxaziridine 76 and methyl iodide: test for *O*-transfer[186]

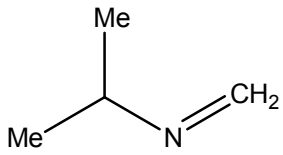


62 **77a, n = 1**
77b, n = 2

N-Benzyloxaziridine (*ca.* 1.35 g in 3 ml dichloromethane, 10 equiv.) was added to 20 ml scintillation vial charged with a solution of *N,N*'-dimethylethylenethiourea (130 mg, 1 mmol) in benzene (1 ml), capped and stirred for a few minutes. Methyl iodide (0.68 ml, 11 equiv.) was then added to the reaction mixture and stirred overnight at RT. The resultant orange-brown suspension was filtered and the filtrate was concentrated *in vacuo*.

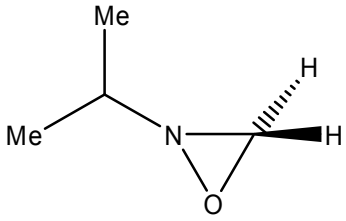
The proton and carbon NMR spectra of the filtrate were complex and only *N,N'*-dimethylimidazolidin-2-one **67** could be identified. The precipitate gave complex ^{1}H and ^{13}C NMR spectra.

_N_-Isopropylmethyleneamine 78



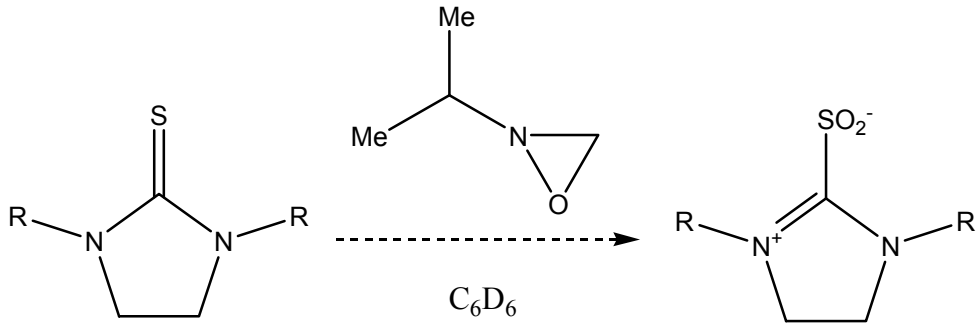
Following a literature procedure,[214] formaldehyde solution (0.89 ml, 32% w/w, 1.2 equiv.) was added drop wise to isopropylamine (0.86 ml, 10 mmol) cooled over a water bath. The resultant emulsion was stirred under a nitrogen atmosphere for 2 h. Potassium hydroxide pellets (*ca.* 2 g) were added to the mixture and left to stand for ½ h. The top layer was separated from the biphasic mixture and filtered. The resultant colourless liquid (1.47 g, crude) was identified as *N*-isopropylmethyleneamine and of sufficient purity to be used for subsequent oxaziridine preparation. ν_{max}(neat)/cm^{-1} 2965, 1461; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.06 (6H, d, *J* 6.5, CH_3), 2.85 (1H, septuplet, *J* 6.5, CH), 3.53 (2H, br s, N=CH_2); δ_H(300 MHz; C_6D_6; Me_4Si) 1.00 (6H, d, *J* 6.5, CH_3), 2.83 (1H, septuplet, *J* 6.5, CH), 3.52 (2H, br s, CH_2); δ_C(75 MHz; $CDCl_3$; Me_4Si) 19.9 (CH_3), 49.8 (CH) and 68.5 (CH_2); δ_C(75 MHz; C_6D_6; Me_4Si) 19.4 (CH_3), 49.3 (CH) and 68.3 (CH_2); *m/z* (LSIMS) 72 (MH^+, 100%).

_N_-Isopropyloxaziridine 79



Peracetic acid solution (1.09 ml, 32% w/w, 1.2 equiv.) was added to a solution of *N*-isopropylmethyleneamine **78** (356 mg, 5 mmol) in dichloromethane (10 ml) cooled over an ice-bath. The resultant solution was stirred for 45 min at RT. The solution was partitioned over water and separated. The organic layer was washed with saturated sodium carbonate, dried (magnesium sulfate) and concentrated to remove most of the dichloromethane to afford *ca.* 2 ml of a colourless solution. The product was treated as a solution and used within 1 day. The solution tested positive for peroxides with sodium iodide/acetic acid/acetone (*ca.* 5 mg/2 drops/5 ml quantities, respectively). NMR spectroscopic analysis of the product revealed a mixture of compounds and was found to give resolved peaks in d_6-benzene. All peaks in the NMR spectra were assigned with the aid of COSY and HMQC experiments. δ_H(300 MHz; C_6D_6; Me_4Si) 0.76 (3H, d, *J* 6.5, CH_3), 1.17 (3H, d, *J* 6.5, CH_3), 1.63 (1H, septuplet, *J* 6.5, C*H*Me_2), 2.86 (1H, d, *J* 10.5, OCH_2), 3.43 (1H, d, *J* 10.5, OCH_2); δ_C(75 MHz; C_6D_6; Me_4Si) 17.9, 21.0 (2xCH_3), 62.5 (*C*HMe_2) and 70.1 (OCH_2).

General procedure for the oxidation of substituted thioureas with *N*-isopropyloxaziridine 79: NMR studies

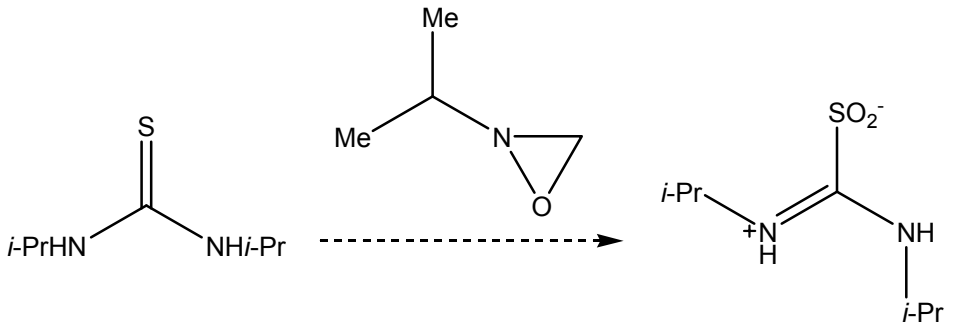


The thiourea (0.077 mmol) was dissolved in d_6-benzene (0.5 ml) and analysed by proton NMR. *N*-Isopropyloxaziridine **79** (crude; dichloromethane solution) in d_6-benzene was then added to the thiourea solution and sonicated at RT for 30 min. Proton, carbon and HMQC NMR spectroscopic analyses were performed to monitor the reaction. The NMR tubes were then heated over a water bath (water temperature 35 °C) for 3 h. Additional heating of the samples (water temperature 40 °C) for 6 h resulted in no further change as determined from NMR spectroscopic studies. Unreacted oxaziridine was identified by NMR spectroscopic in all experiments.

a) *N,N'*-Dimethylethylenethiourea **62** (10 mg, 0.077 mmol) was reacted with *N*-isopropyloxaziridine **79** (*ca.* 30 mg in 2 ml dichloromethane, 2 equiv.) following the general procedure. NMR spectroscopic analysis was inconclusive. Peaks in the ^{1}H and ^{13}C NMR spectra could not be assigned. NMR spectroscopic data at t = 30 min: δ_H(300 MHz; C_6D_6; Me_4Si) 2.40 (1H, s, couples with ^{13}C at 47.6 ppm) and 2.80 (1.5H, s, couples with ^{13}C at 34.8 ppm); NMR spectroscopic data at t = 3 h: δ_H(300 MHz; C_6D_6; Me_4Si) 2.40 (1H, s, couples with ^{13}C at 47.5 ppm), 2.42 (0.2H, s, couples with ^{13}C at 31.4 ppm), 2.51 (1H, s, couples with ^{13}C at 31.4 ppm) and 2.80 (1.5H, s, couples with ^{13}C at 34.8 ppm). NMR spectroscopic data at t = 6 h was identical to the data obtained at t = 3 h.

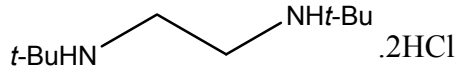
b) *N,N'*-Diisopropylethylenethiourea **63** (14 mg, 0.077 mmol) was reacted with *N*-isopropyloxaziridine **79** (*ca.* 30 mg in 2 ml dichloromethane, 2 equiv.) following the general procedure. NMR spectroscopic analysis of the reaction revealed that *N,N'*-diisopropylethylenethiourea was unreactive towards *N*-isopropyloxaziridine as evident from the identification of starting materials at t = 30 min, t = 3 h and t = 6 h.

Reaction of *N,N'*-diisopropylthiourea with *N*-isopropyloxaziridine 79



N-Isopropyloxaziridine **79** (*ca.* 790 mg in 5 ml dichloromethane, 2 equiv.) was added to a solution of *N,N'*-diisopropylthiourea (160 mg, 1 mmol) in tetrahydrofuran (5 ml) cooled over an ice bath. The solution was stirred under a nitrogen atmosphere for 2½ h at RT and then concentrated *in vacuo* to yield a buff solid. NMR and TLC analysis revealed the presence of starting thiourea and other unidentifiable products. *N*-Isopropyloxaziridine and the corresponding imine were not identified in the NMR spectra.

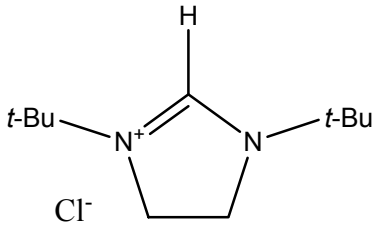
***N,N'*-Di-*tert*-butylethylenediamine dihydrochloride 80**



Following a literature procedure,[177] 1 M hydrochloric acid (47 ml, 2 equiv.) was added to a flask charged with *N,N'*-di-*tert*-butylethylenediamine (5 ml, 23.24 mmol) at RT and stirred for 1 h. The colourless solution was concentrated *in vacuo* to a white solid and dried (50 ºC, 0.3 mbar) for 2 h to furnish a white crystalline solid (5.98 g, 99%) identified as the title salt, when compared with literature data.[177] δ_H(300 MHz; DMSO; Me_4Si) 1.30

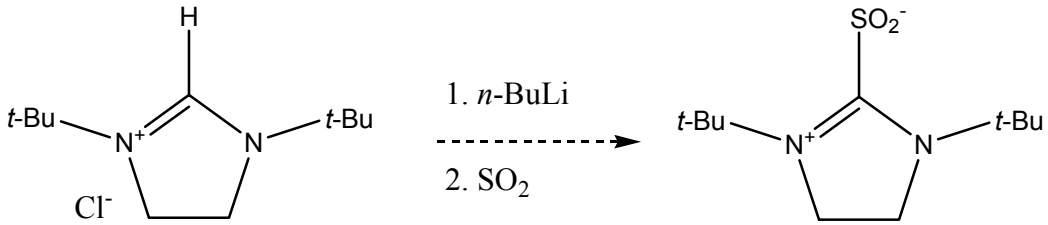
(18H, s, CH_3), 3.31 (4H, br m, CH_2), 9.64 (4H, br m, NH); δ_C(75 MHz; DMSO; Me_4Si) 24.9 (Me), 37.4 (CH_2) and 56.6 (C_q).

***N,N'*-Di-*tert*-butylimidazolinium chloride 81**



Following a literature procedure,[177] a few drops of formic acid were added to a suspension of *N,N'*-di-*tert*-butylethylenediamine dihydrochloride **80** (1.6 g, 6.52 mmol) in triethyl orthoformate (10.8 ml, 10 equiv.) at RT and then heated to reflux over an oil bath (oil temperature 115 ºC) overnight. The colourless solution was cooled to RT and concentrated *in vacuo* to yield a white crystalline solid (1.25 g, 88%) identified as the title salt, in agreement with literature data.[177] δ_H(300 MHz; DMSO; Me_4Si) 1.37 (18H, s, CH_3), 3.93 (4H, s, CH_2), 8.24 (1H, s, CH); δ_C(75 MHz; DMSO; Me_4Si) 27.4 (CH_3), 44.8 (CH_2), 56.0 (C_q) and 153.1 (CH); *m/z* (LSIMS) 183 (M^+ - Cl, 100%).

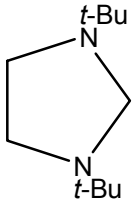
Adduct 9 formation from *N,N'*-di-*tert*-butylimidazolin-2-ylidene 82 and SO_2: deprotonation with *n*-butyllithium



9

Carbene **82** was prepared by following a literature procedure[166] (step 1) and is as follows. *n*-Butyllithium (2.5 M in hexane, 0.8 ml, 1 equiv.) was added to a suspension of *N,N'*-di-*tert*-butylimidazolinium chloride **81** (438 mg, 2 mmol) in dry *n*-pentane at RT and stirred

for 1 h under a nitrogen atmosphere. The white suspension was then transferred *via* cannula through an oven dry Schlenk frit to give a pale-yellow filtrate. *n*-Pentane was then evaporated *in vacuo* (RT, 0.3 mbar) to yield a colourless wax (102 mg, 56% crude) identified as the carbene, ***N,N'*-di-*tert*-butylimidazolin-2-ylidene 82**, in agreement with literature data.[173]

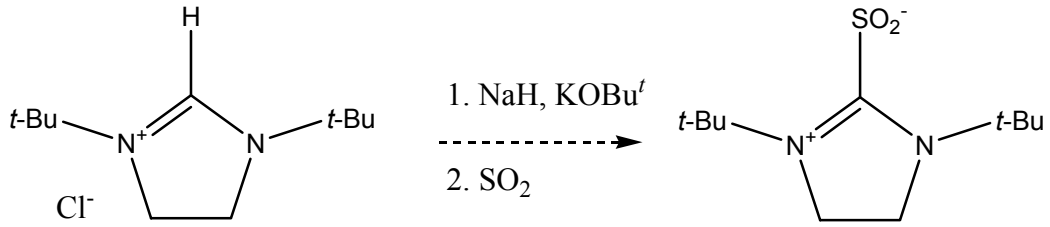


82

A saturated *ca.* 100 mg ml^{-1} concentration was required to detect the carbenic carbon. δ_H(300 MHz; C_6D_6; Me_4Si) 1.35 (18H, s, CH_3), 3.02 (4H, s, CH_2); δ_C(100 MHz; C_6D_6; Me_4Si) 29.9 (CH_3), 44.5 (CH_2), 53.9 (CMe_3) and 238.3 (C:). The NMR spectra of carbene **82** remained unchanged when analysed again after standing at RT for 2 days.

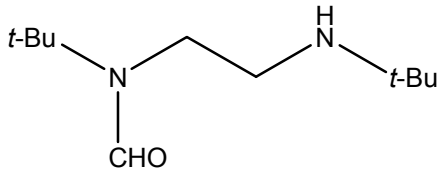
Adduct **9** formation (step 2) was attempted, by following a literature procedure[47] and is as follows. The carbene **82** was dissolved in dry tetrahydrofuran (10 ml) and bubbled with sulfur dioxide gas at RT for 2 min. The sulfur dioxide addition resulted in an immediate formation of a yellow suspension. The sulfur dioxide gas supply was removed and the reaction mixture sealed and stirred at RT for 2 h. The buff suspension (15 mg) was filtered but was not thought to consist of any organic product as evident from the blank ^{1}H NMR spectrum in d_6-benzene. The filtrate was concentrated *in vacuo* (RT, 0.3 mbar) to an orange solid and identified as a *N,N'*-di-*tert*-butylimidazolinium salt (55 mg, crude), insoluble in d_6-benzene. δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.44 (18H, s, CH_3), 4.00 (4H, s, CH_2), 8.31 (1H, s, CH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 27.1 (CH_3), 44.3 (CH_2), 56.0 (C_q) and 151.2 (CH).

Adduct formation from *N,N'*-di-*tert*-butylimidazolin-2-ylidene 82 and SO_2: deprotonation with sodium hydride/potassium *tert*-butoxide



Step 1, carbene **82** formation (literature procedure[177]): an oven dry Schlenk tube was charged with *N,N'*-di-*tert*-butylimidazolinium chloride **81** (656 mg, 3 mmol), sodium hydride (240 mg, 60% dispersion in mineral oil, 4 equiv.) and potassium *t*-butoxide (9 mg, 5 mol%). The reaction solids were flame dried (60 ºC, 0.3 mbar) and then purged with dry nitrogen (pre-dried by passing over potassium hydroxide pellets and silica gel) for 1 h. Dry tetrahydrofuran (10 ml) was then added, resulting in concomitant evolution of hydrogen gas. The suspension was stirred under a nitrogen atmosphere at RT overnight. The faint blue suspension was filtered, *via* cannula transfer, through a celite pad (celite, pre-treated: soaked in concentrated hydrochloric acid, overnight; then washed with water, methanol and flame dried 50 ºC, 0.3 mbar) to give *ca.* 50 ml colourless filtrate. A 10 ml aliquot was extracted and concentrated (RT, 0.3 mbar). Step 2, adduct formation (literature procedure[47]): the remainder of the filtrate was bubbled with a slow stream of sulfur dioxide gas at RT for 1 min and immediately gave a yellow solid suspended in a green supernatant. The addition of sulfur dioxide was accompanied with mild exotherm (40 ºC). The sulfur dioxide gas supply was removed and the suspension immediately concentrated *in vacuo* (RT, 0.3 mbar) to afford a yellow solid (60 mg).

- Aliquot**:** Mixture of carbene **82**:formamide **83** (2.5:1, as deduced by ^{1}H NMR spectroscopy). Only the ring-opened formamide, ***N*-formyl-*N,N'*-di-*tert*-butylethylenediamine 83** peaks (compared with literature data[166]) are listed.



83

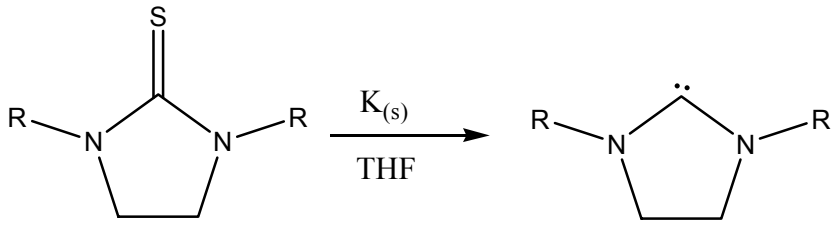
δ_H(300 MHz; C_6D_6; Me_4Si) 0.86 (9H, s, CH_3), 1.03 (9H, s, CH_3), 2.68-2.76 (2H, m, CH_2), 3.30-3.35 (2H, m, CH_2), 8.40 (1H, s, CH); δ_C(75 MHz; C_6D_6; Me_4Si) 29.2, 29.4 (2xCH_3), 42.3, 43.1, (2xCH_2), 53.9 (C_q) and 161.1 (C=O).

- Yellow solid: Poor solubility in d_6-benzene therefore analysed in d_1-chloroform. A *N,N'*-di-*tert*-butylimidazolinium salt was detected when the NMR spectra were compared with the NMR spectra of the salt formed from the oxidation of thiourea **64** with *meta*-chloroperbenzoic acid. The counter anion is unknown. δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.48 (18H, s, CH_3), 4.07 (4H, s, CH_2), 7.98 (1H, s, CH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 27.9 (CH_3), 45.2 (CH_2) and 152.6 (CH).

An attempt with prolonged sulfur dioxide gas exposure (5 min, 0 ºC) gave green, followed by orange and then brown solutions which, following the same work-up procedure, was thought to yield a *N,N'*-di-*tert*-butylimidazolinium salt (as judged by NMR spectroscopy).

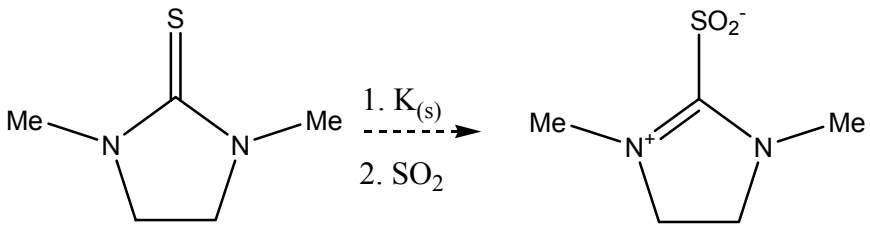
When the procedure was repeated with some modification (layering of the yellow suspension with dry *n*-hexane,[47] after sulfur dioxide exposure) no adduct could be isolated. Instead, the product mixture was thought to compose of the *N,N'*-di-*tert*-butylimidazolinium salt, as judged by NMR spectroscopy.

General procedure[173] for the desulfurisation of ethylenethiourea derivatives



Potassium (3 equiv.) was added to a solution of *N,N'*-dialkylethylenethiourea (2.5 mmol) in dry tetrahydrofuran (5 ml) at RT under a nitrogen atmosphere. The mixture was refluxed under a nitrogen atmosphere over an oil bath (oil temperature 85 ºC) for 1 h. The blue-green suspension was cooled to RT and filtered over a flame dry Schlenk frit to give a pale-yellow filtrate. A 1 ml aliquot was extracted and concentrated (-20 ºC, 0.3 mbar) to give a yellow oil and analysed by NMR spectroscopy (the remaining filtrate was immediately bubbled with sulfur dioxide gas, required for the next stage[47] adduct formation).

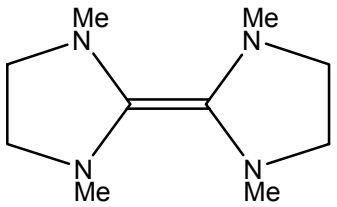
Adduct formation from *N,N'*-dimethylimidazolin-2-ylidene 84 and SO_2: desulfurisation with potassium



The general desulfurisation procedure was followed using potassium (294 mg, 3 equiv.) and *N,N'*-dimethylethylenethiourea **62** (325 mg, 2.5 mmol). Adduct formation: a slow stream of sulfur dioxide was passed over the filtrate for 1 min at RT. An immediate formation of a red-brown suspension took place. The sulfur dioxide supply was removed and the reaction mixture stirred under a nitrogen atmosphere at RT for 1 h. The

suspension was filtered through a flame dry Schlenk frit and the filtrate concentrated (RT, 0.3 mbar) to afford buff solid (110 mg).

- Aliquot**: *N,N',N,N'*-Tetramethyl-2,2'-biimidazolidinylidene 85** (in agreement with literature data[173])

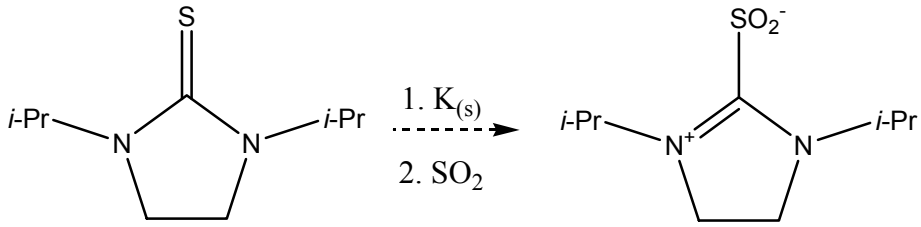


85

Other unknown peaks listed from the complex NMR spectrum. Tetraazafulvalene peaks are italicised. δ_H(300 MHz; C_6D_6; Me_4Si) 2.52-2.56 (24H, m, includes tetraazafulvalene CH_3), *2.74* (4H, s, CH_2), *2.81* (4H, s, CH_2); δ_C(75 MHz; C_6D_6; Me_4Si) 32.5, 36.3, *39.7* (3xCH_3), 44.8, 47.6, *52.6* (3xCH_2), 105.4, *129.5* (C=C) and 161.5. The desired carbene **84** could not be detected.

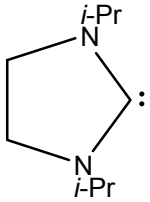
- Buff solid: unknown; neither starting material **62**, *N,N'*-dimethylimidazolidin-2-one **67** nor *N,N',N,N'*-tetramethyl-2,2'-biimidazolidinylidene **85** were detected. All characterization data of the unknown mixture are provided. ν_{max}/cm^{-1} 2923-2851 (CH), 1499, 1110-1014; δ_H(300 MHz; C_6D_6; Me_4Si) 2.47 (3H, s), 2.52 (2H, s), 2.81 (3H, s); δ_C(75 MHz; C_6D_6; Me_4Si) 32.1, 35.4 (2xCH_3), 45.3 and 48.2 (2xCH_2); Major MS peaks (cationic) are listed but could not be assigned: *m/z* (LSIMS) 204 (100%), 183 (5), 131 (5), 117 (60); The buff solid remained unchanged after 8 d on standing at RT, by all analyses except ^{1}H NMR spectroscopy: δ_H(300 MHz; C_6D_6; Me_4Si) 2.47 (1H, s), 2.48 (2.3H, s), 2.52 (2.8H, s), 2.82 (3.6H, s).

Adduct formation from *N,N'*-diisopropylimidazolin-2-ylidene 86 and SO_2: desulfurisation with potassium



The general desulfurisation procedure was followed with potassium (1.17 g, 3 equiv.) and *N,N'*-diisopropylethylenethiourea **63** (1.86 g, 10 mmol). A slow stream of sulfur dioxide was passed over the filtrate for 1 min at RT. An immediate formation of a red-brown suspension took place. The suspension was filtered over a flame dry Schlenk frit to give a yellow filtrate and then concentrated *in vacuo* (RT, 0.3 mbar) to an orange gum (240 mg).

- Aliquot: ***N,N'*-Diisopropylimidazolin-2-ylidene 86** (in agreement with literature data[173])



86

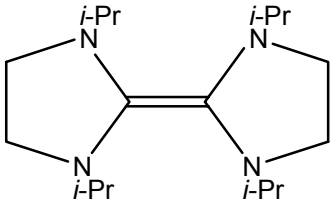
A 90 mg ml^{-1} concentration in d_6-benzene was required to detect the carbenic centre at RT. The carbenic peak was found to resonate in the same phase as a quaternary/secondary ^{13}C signal. δ_H(300 MHz; C_6D_6; Me_4Si) 1.10 (12H, br d, *J* 6.0, CH_3), 2.92 (4H, br s, CH_2), 3.87 (2H, br m, CH); δ_C(75 MHz; C_6D_6; Me_4Si) 22.1 (CH_3), 44.6 (CH_2), 50.6 (CH) and 236.4 (C:).

- Orange gum: Crude product poorly soluble in d_6-benzene. NMR revealed one compound as a major product, thought to be the target carbene-sulfur dioxide

adduct, *N,N'*-diisopropylethylenethiourea dioxide **66**. ν_{max}/cm^{-1} 2971 (CH), 1639 (C=N), 1264-1126 (SO_2 or SO_3 stretching); δ_H(300 MHz; $CDCl_3$; Me_4Si), 1.20 (12H, br d, *J* 6.6, CH_3), 3.81 (4H, br s, CH_2), 4.19 (2H, septuplet, *J* 6.6, CH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 20.6 (CH_3), 44.1 (CH_2) and 49.9 (CH); *m/z* (LSIMS) 297 ($[M+K_2]^+$, 100%), 257 ($[M+K]^+$, 90).

Residual tetrahydrofuran was evaporated under a stream of nitrogen overnight to furnish a compound which was found to have decomposed to a *N,N'*-diisopropylimidazolinium salt; the counter-anion is unknown. δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.27 (12H, d, *J* 6.8, CH_3), 3.88 (4H, s, CH_2), 4.19 (2H, septuplet, *J* 6.8, CH), 8.64 (1H, s, CH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 20.5 (CH_3), 44.3 (CH_2) 50.0 and 156.4 (2xCH).

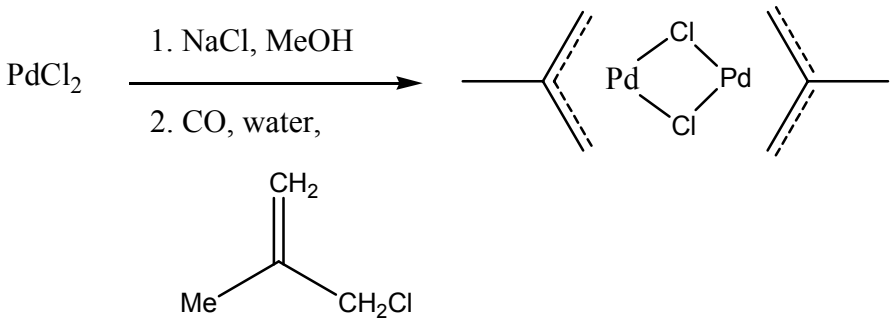
***N,N',N,N'*-Tetraisopropyl-2,2'-biimidazolidinylidene 87**



87

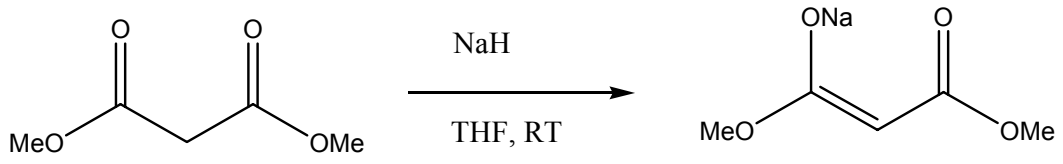
A separate attempt to isolate *N,N'*-diisopropylimidazolin-2-ylidene **86**, following the above desulfurisation procedure, furnished the carbene **86** as a yellow oil (1.4 g, 91%, crude). Carbene **86**, in d_6-benzene, was found to dimerise at RT within *ca.* 2 h. NMR spectroscopic data of the dimer, *N,N',N,N'*-tetraisopropyl-2,2'-biimidazolidinylidene **87**, are provided and is in agreement with literature data:[173] δ_H(400 MHz; C_6D_6; Me_4Si) 1.04 (12H, d, *J* 6.5, CH_3), 2.75 (4H, s, CH_2), 4.08 (2H, septuplet, *J* 6.5, CH); δ_C(100 MHz; C_6D_6; Me_4Si) 19.7 (CH_3), 43.1 (CH_2), 46.3 (CH) and 124.3 (C=C).

Bis(methallyl)dichlorodipalladium(II) 88



Following a literature procedure,[200] a Schlenk tube was charged with palladium(II) chloride (4.44 g, 25 mmol), sodium chloride (2.96 g, 2 equiv.), methanol (60 ml) and water (20 ml) and stirred at RT for ½ h. β-Methallyl chloride (7.68 ml, 3.16 equiv.) was added the resultant red-brown solution and sealed. Carbon monoxide gas was bubbled through the solution for 1 h resulting in a yellow suspension. The mixture was vented in a fume cupboard and bubbled with nitrogen overnight. The mixture was poured onto water (300 ml) and extracted with chloroform (300 ml). The organic layer was washed with water (100 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo* to a yellow solid. Recrystallisation from chloroform/petroleum ether (40:60) furnished yellow needles (3.87 g, 39%) identified as bis(methallyl)dichlorodipalladium(II), in agreement with literature data.[200] δ_H(300 MHz; C_6D_6; Me_4Si) 1.40 (3H, s, CH_3), 2.33 (2H, s, CH_2), 3.41 (2H, s, CH_2); δ_C(75 MHz; C_6D_6; Me_4Si) 22.1 (CH_3), 61.2 and 126.1 (2xCH_2); *m/z* (EI) 393 (M^+), 358 (M^+ - Cl), 303 ($M^+ – CH_2{=}CMe_2Cl$).

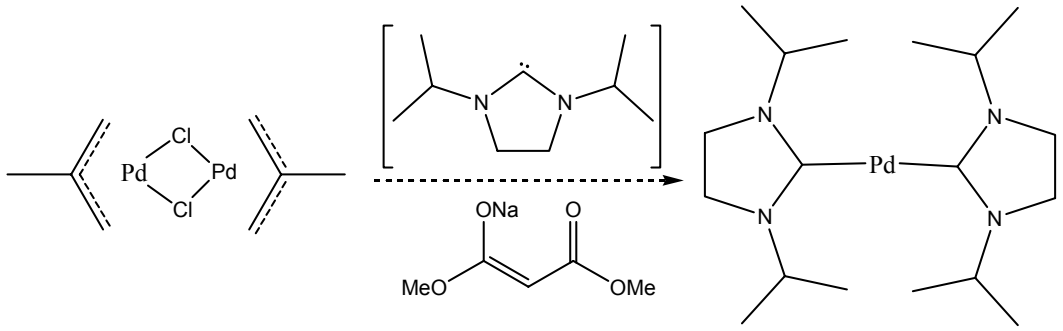
Sodium dimethylmalonate



Following a literature procedure,[199] a slurry of sodium hydride (1.08 g, 60% dispersion in mineral oil, 1.17 equiv.) in tetrahydrofuran (10 ml) was added drop wise over 1 h to a

solution of dimethylmalonate (2.6 ml, 22.7 mmol) in tetrahydrofuran (20 ml) cooled to 5 °C. The reaction was then brought to RT and stirred under a nitrogen atmosphere for 3 h. The suspension was filtered through a celite pad and the filtrate concentrated *in vacuo* to a buff solid. The crude solid was dried *in vacuo* (50 °C, 0.3 mbar) to give a buff amorphous solid (4.15 g) which was found to contain no tetrahydrofuran by NMR spectroscopy.

General procedure[199] for the synthesis of bis(1,3-diisopropylimidazol-2-ylidene)palladium(0) 90



90

The formation of the complex **90** was carried out, using either carbene **86** or the carbene precursor **66,** as the carbene source.

The carbene source (2 equiv.) in tetrahydrofuran (10 ml) was added to a Schlenk tube charged with bis(methallyl)di-chloro-di-palladium(II) **88** (985 mg, 2.5 mmol), sodium dimethylmalonate (771 mg, 2 equiv.) and stirred under reflux over an oil bath (oil temperature 80 ºC) under a nitrogen atmosphere overnight. The reaction was cooled to RT and the solvent removed (RT, 0.3 mbar) maintaining a nitrogen atmosphere throughout. Dry toluene was added and the black-brown suspension was filtered through a celite pad (celite pre-treated with concentrated hydrochloric acid, overnight; washed with water, methanol and then flame dried at 50 ºC, 0.3 mbar). The brown filtrate was concentrated *in vacuo* (RT, 0.3 mbar).

a) *N,N'*-Diisopropylimidazolin-2-ylidene **86** (771 mg, crude, 2 equiv.) was utilised as the carbene source following the general procedure to furnish a dark-brown oil (560 mg). The complex NMR spectra in d_6-benzene could not be interpreted; the starting carbene was not detected.

b) *N,N'*-Diisopropylethylenethiourea dioxide **66** (1.09 g, crude, 2 equiv.) was utilised as the carbene source following the general procedure to furnish a brown gum (489 mg). The product could not be identified by NMR spectroscopy (in d_6-benzene) and was too complex to interpret.

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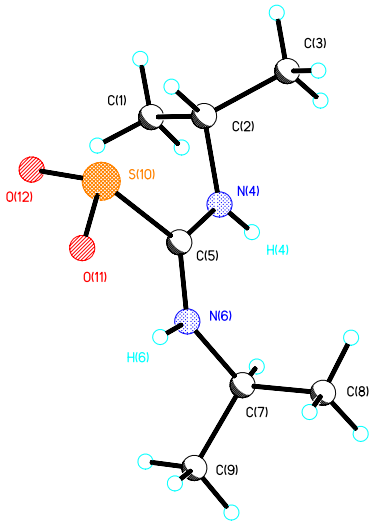
Appendix

X-ray crystallographic data for *N,N*'-diisopropylthiourea dioxide 25



$C_7H_{16}N_2O_2S$, M = 192.28, monoclinic, β = 109.001 (6)°, a = 9.943(4), b = 10.311(4), c = 10.540(4) Å, U = 1021.8(6) Å^3, T = 180 K, space group $P2_1/n$ (No 14), μ(Mo-Kα) = 1.978 mm^{-1}, Z = 4, λ = 0.71073 Å, 9920 reflections measured, 2553 unique [R(int) = 0.0747], R1[for 2172 reflections with I>2sigma(I)] = 0.0397, wR2 = 0.1101, T_{min} 0.8185, T_{max} 0.9879, $\mu(Mo_{K\alpha})$ = 0.068 mm^{-1}. Data / restraints / parameters 2553/ 2/ 119 refined against F^2 (SHELXTL)[b]. Largest difference Fourier peak and hole 0.592 and -0.224 e.Å^{-3}

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for *N,N*'-diisopropylthiourea dioxide **25**. U(eq) is defined as one third of the trace of the orthogonalised Uij tensor:

	x	y	z	U(eq)
C(1)	627(2)	3390(2)	2818(2)	62(1)
C(2)	809.2(16)	2900.3(16)	1524.4(17)	38(1)
C(3)	63(2)	1626(2)	1075(2)	57(1)
N(4)	2347.2(12)	2751.5(11)	1741.8(12)	28(1)
C(5)	3102.8(14)	3572.9(12)	1310.0(12)	24(1)
N(6)	4472.6(12)	3519.1(11)	1550.4(12)	28(1)
C(7)	5463.6(15)	2537.8(14)	2353.4(14)	31(1)
C(8)	5735(2)	1526.2(18)	1428(2)	55(1)
C(9)	6817.7(18)	3225(2)	3171.5(18)	49(1)
S(10)	2211.2(4)	5000.9(3)	211.1(3)	27(1)
O(11)	3459.5(13)	5505.1(12)	-106.7(12)	44(1)
O(12)	1850.7(12)	5806.3(10)	1226.9(11)	35(1)

[b] G. M. Sheldrick, *SHELXTL Ver 5.1*, Bruker Analytical X-ray Systems, **1997**.

Selected bond lengths [Å] and bond angles [º] for *N,N'*-diisopropylthiourea dioxide **25**:

C(1)-C(2)	1.519(3)	N(4)-C(2)-C(3)	109.69(14)
C(2)-N(4)	1.4786(19)	N(4)-C(2)-C(1)	108.35(15)
C(2)-C(3)	1.507(3)	C(3)-C(2)-C(1)	112.41(17)
N(4)-C(5)	1.3082(18)	C(5)-N(4)-C(2)	124.13(12)
N(4)-H(4)	0.863(15)	C(5)-N(4)-H(4)	121.5(13)
C(5)-N(6)	1.3028(18)	C(2)-N(4)-H(4)	113.7(13)
C(5)-S(10)	1.9045(14)	N(6)-C(5)-N(4)	125.96(12)
N(6)-C(7)	1.4724(17)	N(6)-C(5)-S(10)	113.66(10)
N(6)-H(6)	0.874(15)	N(4)-C(5)-S(10)	120.38(10)
C(7)-C(8)	1.512(2)	C(5)-N(6)-C(7)	127.05(11)
C(7)-C(9)	1.518(2)	C(5)-N(6)-H(6)	116.0(13)
S(10)-O(12)	1.4881(11)	C(7)-N(6)-H(6)	116.7(13)
		N(6)-C(7)-C(8)	109.27(12)
		N(6)-C(7)-C(9)	108.03(13)
		C(8)-C(7)-C(9)	112.16(15)
		O(11)-S(10)-O(12)	112.50(7)
		O(11)-S(10)-C(5)	98.66(6)
		O(12)-S(10)-C(5)	99.63(6)

Symmetry transformations used to generate equivalent atoms:

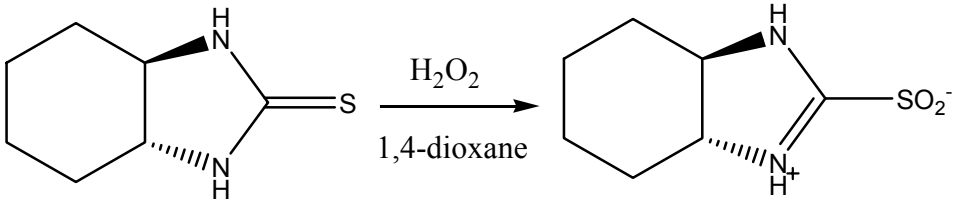
Anisotropic displacement parameters (A^2 x 10^3) for *N,N'*-diisopropylthiourea dioxide **25**. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]:

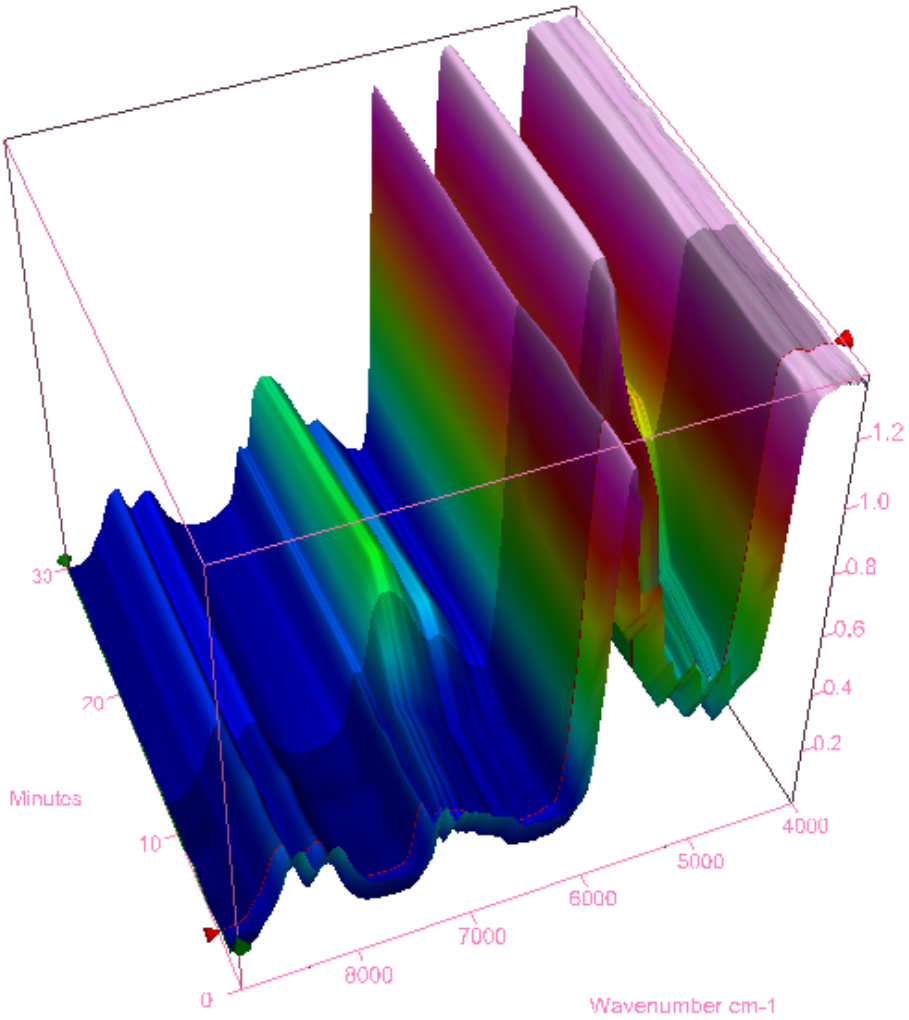
	U11	U22	U33	U23	U13	U12
C(1)	56(1)	68(1)	79(1)	13(1)	46(1)	22(1)
C(2)	22(1)	42(1)	51(1)	16(1)	14(1)	5(1)
C(3)	32(1)	59(1)	72(1)	18(1)	6(1)	-14(1)
N(4)	23(1)	28(1)	33(1)	7(1)	9(1)	4(1)
C(5)	26(1)	22(1)	23(1)	0(1)	9(1)	3(1)
N(6)	25(1)	27(1)	33(1)	8(1)	11(1)	2(1)
C(7)	25(1)	34(1)	35(1)	14(1)	12(1)	5(1)
C(8)	69(1)	38(1)	61(1)	13(1)	27(1)	23(1)
C(9)	29(1)	67(1)	43(1)	21(1)	3(1)	-6(1)
S(10)	29(1)	25(1)	28(1)	4(1)	8(1)	5(1)
O(11)	42(1)	40(1)	56(1)	23(1)	25(1)	10(1)
O(12)	36(1)	27(1)	41(1)	-5(1)	12(1)	4(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for *N,N'*-diisopropylthiourea dioxide **25**:

	x	y	z	U(eq)
H(1A)	1108	4228	3058	93
H(1B)	1044	2764	3539	93
H(1C)	-388	3493	2693	93
H(2A)	411	3560	805	45
H(3A)	187	1362	227	86
H(3B)	-954	1725	947	86
H(3C)	469	964	1759	86
H(4)	2740(20)	2137(17)	2293(17)	41
H(6)	4820(20)	4089(17)	1132(19)	41
H(7A)	5026	2111	2976	37
H(8A)	4832	1129	897	82
H(8B)	6371	857	1961	82
H(8C)	6180	1937	825	82
H(9A)	7523	2583	3659	73
H(9B)	6609	3814	3813	73
H(9C)	7196	3723	2571	73

Near-IR spectrum, monitoring the oxidation of *trans*-4,5-tetramethyleneimidazolidin-2-thione





Density Functional Theory DFT data

All geometries were optimised with restricted B3LYP functional, without constraints. GaussView 3.0 used to display optimised structures. Atoms are represented by colour: sulfur (yellow), nitrogen (blue), oxygen (red), carbon (grey) and hydrogen (white).

A. Basis set investigations of thiourea dioxide 3

All structures characterised by C1 point group; symmetric ν_s and asymmetric ν_{as} stretching modes [cm^{-1}], and bond lengths [Å] listed.

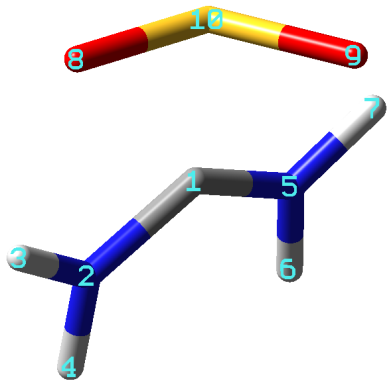
Basis		$\upsilon_s(SO_2)$	$\upsilon_{as}(SO_2)$	S-O		C-S
Gas phase:						
6-31G	d, p	1020	1169	1.51417	1.49972	2.01849
	2d, p	1014	1170	1.49802	1.48194	2.03822
	3d, p	1037	1179	1.49107	1.47905	2.01063
	df, p	1037	1182	1.50811	1.49516	2.01021
	2df, p	1055	1220	1.48821	1.47111	2.08490
	3d, 2pd	1037	1178	1.49095	1.47917	2.01222
	df, 2pd	1034	1180	1.50945	1.4955	2.00479
	2df, 2pd	1048	1210	1.49053	1.47381	2.05096
	3df, 3pd	1055	1200	1.48532	1.47347	2.01936
6-31+G	d, p	1008	1126, 1143	1.51561	1.50211	2.03545
	2d, p	996	1118, 1138	1.50138	1.48866	2.01411
	3d, p	1025	1163	1.4934	1.48058	2.02400
	df, p	1024	1154	1.51004	1.49796	2.02444
	2df, p	1038	1174	1.49217	1.47991	2.03740
	3d, 2pd	1026	1164	1.49326	1.48049	2.02150
	df, 2pd	1022	1154	1.51121	1.49708	2.02867
	2df, 2pd	1036	1173	1.49254	1.48004	2.03552
6-311G	d, p	1038	1187	1.49982	1.48061	2.20783
	2d, p	1048	1199	1.4889	1.47153	2.14525
	3d, p	1048	1198	1.48655	1.47037	2.08133
	df, p	1053	1204	1.49513	1.47727	2.16871
	3d, 2pd	1049	1198	1.48654	1.47046	2.07995
	df, 2pd	1048	1198	1.49715	1.47864	2.14656
	2df, 2pd	1060	1212	1.48628	1.4699	2.10203
6-311+G	d, p	1017	1132, 1152	1.50515	1.4882	2.12569
	2d, p	1026	1159	1.49397	1.48076	2.07262
	3d, p	1037	1173	1.48905	1.47551	2.04655
	df, p	1036	1170	1.49949	1.48498	2.09041
	3d, 2pd	1037	1172	1.48905	1.47583	2.04332
	df, 2pd	1032	1164	1.50097	1.48639	2.07369
	2df, 2pd	1044	1177	1.48994	1.47788	2.04894
IEFPCM solvation:						
Water 6-31+G	d, p	958	1014	1.52935	1.52674	1.93056
	2d, p	953	1016	1.51218	1.51158	1.92156
CH_3CN	d,p	959	1017	1.52958	1.52552	1.93202
	2d, p	954	1019	1.51229	1.51051	1.92394
Water 6-311+G	d, p	952	1002	1.52373	1.52083	1.93957
	2d, p	971	1032	1.50839	1.5073	1.93402
	3d, p	993	1063	1.50124	1.49982	1.92449
	3d, 2p	992	1042, 1063	1.5014	1.50001	1.92366
	df, p	976	1048	1.51542	1.51395	1.93733
	2df, p	993	1064	1.50272	1.50199	1.92932
X-ray[45]		1026, 999	1071	1.4997		1.8592

Basis	C-N		E /hartree	Dipole Moment /D
Gas phase:				
6-31G d, p	1.30498	1.31685	-698.5937579	8.3319
2d, p	1.3012	1.31726	-698.6151026	7.9304
3d, p	1.30428	1.31665	-698.645531	8.3056
df, p	1.30475	1.31548	-698.6099653	8.3685
2df, p	1.30182	1.31772	-698.6351429	7.8319
3d, 2pd	1.30338	1.31633	-698.64854	8.2939
df, 2pd	1.30285	1.31408	-698.6152372	8.3269
2df, 2pd	1.30062	1.31557	-698.6393833	7.9020
3df, 3pd	1.30384	1.31608	-698.6673227	8.3223
6-31+G d, p	1.30658	1.30973	-698.6173208	8.8591
2d, p	1.30348	1.31724	-698.6416446	8.6397
3d, p	1.30496	1.31892	-698.6604078	8.4908
df, p	1.30661	1.31853	-698.6343342	8.9157
2df, p	1.30391	1.31769	-698.6625381	8.6018
3d, 2pd	1.30435	1.31822	-698.6637424	8.4978
df, 2pd	1.3043	1.31771	-698.6391349	8.8496
2df, 2pd	1.30296	1.31689	-698.6666644	8.5874
6-311G d, p	1.30378	1.32047	-698.7015587	7.8997
2d, p	1.30046	1.31707	-698.7318244	7.8846
3d, p	1.30017	1.31638	-698.7463008	8.0210
df, p	1.30092	1.31735	-698.7224848	7.9654
3d, 2pd	1.30025	1.31622	-698.7505699	8.0451
df, 2pd	1.29985	1.31685	-698.7261743	7.9808
2df, 2pd	1.29888	1.31524	-698.7543313	7.9391
6-311+G d, p	1.30362	1.31928	-698.7166894	8.5366
2d, p	1.30088	1.31603	-698.7463197	8.4739
3d, p	1.30148	1.31606	-698.7577295	8.4197
df, p	1.30165	1.31589	-698.7386981	8.6487
3d, 2pd	1.30155	1.31591	-698.7618409	8.4451
df, 2pd	1.30093	1.31531	-698.7419024	8.6440
2df, 2pd	1.30007	1.31467	-698.7692835	8.5103
IEFPCM solvation:				
Water 6-31+G d, p	1.30759	1.31347	-698.6667422	13.1904
2d, p	1.30486	1.3109	-698.6883583	12.8408
CH_3CN d,p	1.30752	1.31379	-698.6648558	13.0328
2d, p	1.30496	1.31128	-698.6865603	12.7026
Water 6-311+G d, p	1.30394	1.31028	-698.7661267	13.2217
2d, p	1.30222	1.30827	-698.7929674	12.8496
3d, p	1.30313	1.30919	-698.8033987	12.7121
3d, 2p	1.30327	1.30936	-698.8056879	12.7102
df, p	1.30233	1.3083	-698.7876265	13.1467
2df, p	1.30167	1.30761	-698.8122987	12.8148
X-ray[45]	1.3096			16.3

B. RB3LYP 6-311+G(3d,p) IEFPCM water calculations

All bond lengths [Å], bond angles [º] and calculated energies [hartree] are listed in tables below structures, in addition to intramolecular hydrogen bond lengths, dipole moment and stretching frequencies.

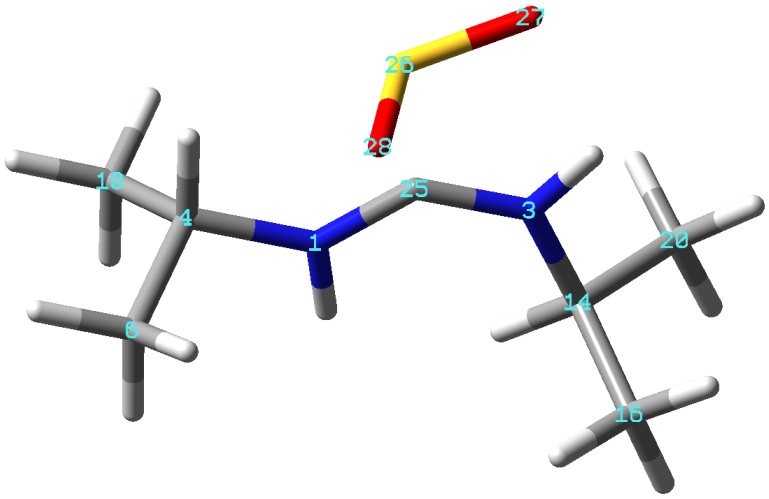
Thiourea dioxide 3



C(1)-N(2)	1.303	N(2)-C(1)-N(5)	125.217
C(1)-N(5)	1.309	N(2)-C(1)-S(10)	116.115
C(1)-S(10)	1.925	N(5)-C(1)-S(10)	118.663
N(2)-H(3)	1.022	C(1)-N(2)-H(3)	117.405
N(2)-H(4)	1.024	C(1)-N(2)-H(4)	123.372
N(5)-H(6)	1.024	H(3)-N(2)-H(4)	119.209
N(5)-H(7)	1.021	C(1)-N(5)-H(6)	122.536
O(8)-S(10)	1.502	C(1)-N(5)-H(7)	120.018
O(9)-S(10)	1.500	H(6)-N(5)-H(7)	117.434
		C(1)-S(10)-O(8)	98.3710
		C(1)-S(10)-O(9)	99.7900
		O(8)-S(10)-O(9)	112.658

Intramolecular H(3)-O(8) bond	2.17452 Å
Dipole moment	12.7121 D
ν_s and ν_{as} /cm^{-1}	993, 1063
E(RB+HF-LYP) =	-698.803398677
Zero-point correction=	0.066300 (Hartree/Particle)
Thermal correction to Energy=	0.073214
Thermal correction to Enthalpy=	0.074158
Thermal correction to Gibbs Free Energy=	0.035120
Sum of electronic and zero-point Energies=	-698.737098
Sum of electronic and thermal Energies=	-698.730185
Sum of electronic and thermal Enthalpies=	-698.729241
Sum of electronic and thermal Free Energies=	-698.768279

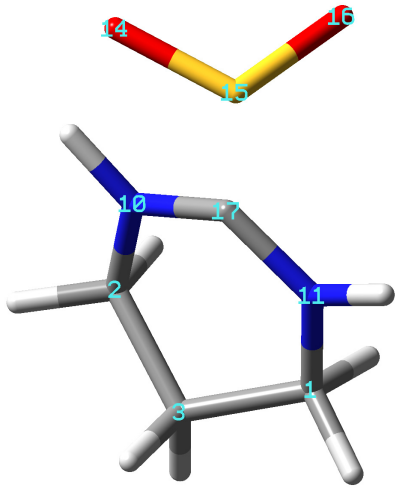
_N,N'_-Diisopropylthiourea dioxide 25



N(1)-C(4)	1.482	C(4)-N(1)-C(25)	125.572
N(1)-C(25)	1.314	H(2)-N(1)-C(4)	114.694
N(1)-H(2)	1.030	H(2)-N(1)-C(25)	119.729
N(3)-C(14)	1.477	C(14)-N(3)-C(25)	128.886
N(3)-C(25)	1.308	C(14)-N(3)-H(24)	118.237
N(3)-H(24)	1.027	H(24)-N(3)-C(25)	112.831
C(4)-C(6)	1.529	N(1)-C(4)-C(6)	109.781
C(4)-C(10)	1.528	N(1)-C(4)-C(10)	109.471
C(14)-C(16)	1.531	C(6)-C(4)-C(10)	112.551
C(14)-C(20)	1.528	N(3)-C(14)-C(16)	110.209
C(25)-S(26)	1.947	N(3)-C(14)-C(20)	109.136
S(26)-O(27)	1.503	C(16)-C(14)-C(20)	112.535
S(26)-O(28)	1.498	N(1)-C(25)-N(3)	126.234
		N(1)-C(25)-S(26)	120.946
		N(3)-C(25)-S(26)	112.818
		C(25)-S(26)-O(27)	97.8030
		C(25)-S(26)-O(28)	99.8720
		O(27)-S(26)-O(28)	112.072

Intramolecular H-O(27) bond	2.0231 Å
Dipole moment	13.0934 D
ν_s and ν_{as} /cm^{-1}	995, 1062
E(RB+HF-LYP) =	-934.743466149
Zero-point correction=	0.235889 (Hartree/Particle)
Thermal correction to Energy=	0.250879
Thermal correction to Enthalpy=	0.251823
Thermal correction to Gibbs Free Energy=	0.193536
Sum of electronic and zero-point Energies=	-934.507577
Sum of electronic and thermal Energies=	-934.492587
Sum of electronic and thermal Enthalpies=	-934.491643
Sum of electronic and thermal Free Energies=	-934.549930

Propylenethiourea dioxide 26



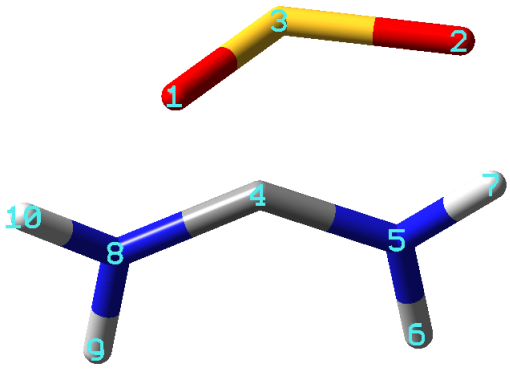
C(1)-C(3)	1.527	C(3)-C(1)-N(11)	109.428
C(1)-N(11)	1.472	C(3)-C(2)-N(10)	109.252
C(2)-C(3)	1.528	C(1)-C(3)-C(2)	110.76
C(2)-N(10)	1.471	C(2)-N(10)-C(17)	122.916
N(10)-C(17)	1.308	C(2)-N(10)-H(12)	120.203
N(10)-H(12)	1.025	H(12)-N(10)-C(17)	116.874
N(11)-C(17)	1.312	C(1)-N(11)-C(17)	122.456
N(11)-H(13)	1.028	C(1)-N(11)-H(13)	118.960
O(14)-S(15)	1.502	H(13)-N(11)-C(17)	118.578
S(15)-O(16)	1.502	O(14)-S(15)-O(16)	112.321
S(15)-C(17)	1.913	O(14)-S(15)-C(17)	98.6480
		O(16)-S(15)-C(17)	99.8620
		N(10)-C(17)-N(11)	122.908
		N(10)-C(17)-S(15)	117.601
		N(11)-C(17)-S(15)	119.490

Intramolecular H-O(14) bond	2.21256 Å
Dipole moment	14.0539 D
ν_s and ν_{as} /cm^{-1}	995, 1055
E(RB+HF-LYP) =	-815.561042915
Zero-point correction=	0.132216 (Hartree/Particle)
Thermal correction to Energy=	0.141070
Thermal correction to Enthalpy=	0.142014
Thermal correction to Gibbs Free Energy=	0.097997
Sum of electronic and zero-point Energies=	-815.428827
Sum of electronic and thermal Energies=	-815.419973
Sum of electronic and thermal Enthalpies=	-815.419029
Sum of electronic and thermal Free Energies=	-815.463046

C. RB3LYP 6-31G(d,p) gas phase calculations

All bond lengths [Å], bond angles [º] and calculated energies [hartree] are listed in tables below structure, in addition to intramolecular hydrogen bond lengths, dipole moment, stretching frequencies, where applicable.

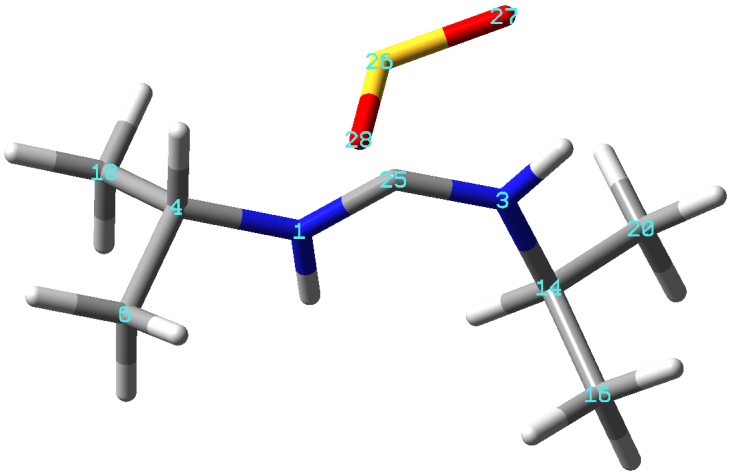
Thiourea dioxide 3



O(1)-S(3)	1.500	O(1)-S(3)-O(2)	117.721
O(2)-S(3)	1.514	O(1)-S(3)-C(4)	97.4930
S(3)-C(4)	2.018	O(2)-S(3)-C(4)	93.8340
C(4)-N(5)	1.305	S(3)-C(4)-N(5)	112.386
C(4)-N(8)	1.317	S(3)-C(4)-N(8)	120.128
N(5)-H(9)	1.050	N(5)-C(4)-N(8)	127.451
N(5)-H(10)	1.050	C(4)-N(5)-H(9)	118.000
H(7)-N(8)	1.050	C(4)-N(5)-H(10)	120.999
H(8)-N(8)	1.050	H(9)-N(5)-H(10)	120.999
		C(4)-N(8)-H(7)	118.000
		C(4)-N(8)-H(8)	120.999
		H(7)-N(8)-H(8)	120.999

Intramolecular H(7)-O(2) bond	1.93878 Å
Dipole moment	8.3319 D
ν_s and ν_{as} /cm^{-1}	1021, 1170
E(RB+HF-LYP) =	-698.593757916
Zero-point correction=	0.068215 (Hartree/Particle)
Thermal correction to Energy=	0.075246
Thermal correction to Enthalpy=	0.076190
Thermal correction to Gibbs Free Energy=	0.036385
Sum of electronic and zero-point Energies=	-698.525543
Sum of electronic and thermal Energies=	-698.518512
Sum of electronic and thermal Enthalpies=	-698.517568
Sum of electronic and thermal Free Energies=	-698.557373

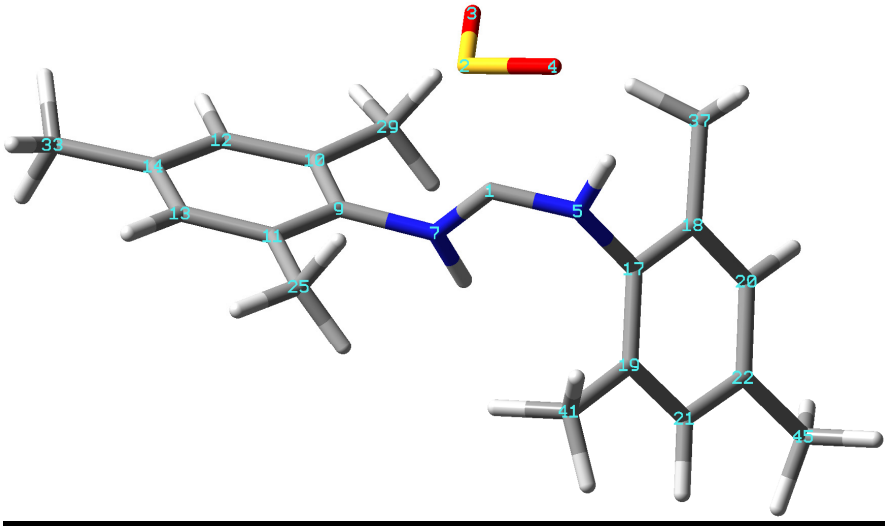
_N,N'_-Diisopropylthiourea dioxide 25



N(1)-C(4)	1.481	C(4)-N(1)-C(25)	124.320
N(1)-C(25)	1.322	H(2)-N(1)-C(4)	115.082
N(1)-H(2)	1.018	H(2)-N(1)-C(25)	119.904
N(3)-C(14)	1.470	C(14)-N(3)-C(25)	129.008
N(3)-C(25)	1.309	C(14)-N(3)-H(24)	121.002
N(3)-H(24)	1.041	H(24)-N(3)-C(25)	109.456
C(4)-C(6)	1.531	N(1)-C(4)-C(6)	110.336
C(4)-C(10)	1.530	N(1)-C(4)-C(10)	108.988
C(14)-C(16)	1.535	C(6)-C(4)-C(10)	113.228
C(14)-C(20)	1.530	N(3)-C(14)-C(16)	110.896
C(25)-S(26)	2.043	N(3)-C(14)-C(20)	108.961
S(26)-O(27)	1.517	C(16)-C(14)-C(20)	112.439
S(26)-O(28)	1.499	N(1)-C(25)-N(3)	125.387
		N(1)-C(25)-S(26)	124.765
		N(3)-C(25)-S(26)	109.647
		C(25)-S(26)-O(27)	93.3640
		C(25)-S(26)-O(28)	98.8630
		O(27)-S(26)-O(28)	115.899

Intramolecular H-O(27) bond	1.80486 Å
Dipole moment	8.3204 D
ν_s and ν_{as} /cm^{-1}	1020, 1158
E(RB+HF-LYP) =	-934.498494242
Zero-point correction=	0.237881 (Hartree/Particle)
Thermal correction to Energy=	0.253078
Thermal correction to Enthalpy=	0.254022
Thermal correction to Gibbs Free Energy=	0.194747
Sum of electronic and zero-point Energies=	-934.260613
Sum of electronic and thermal Energies=	-934.245417
Sum of electronic and thermal Enthalpies=	-934.244472
Sum of electronic and thermal Free Energies=	-934.303747

_N,N'_-Dimesitylthiourea dioxide 31

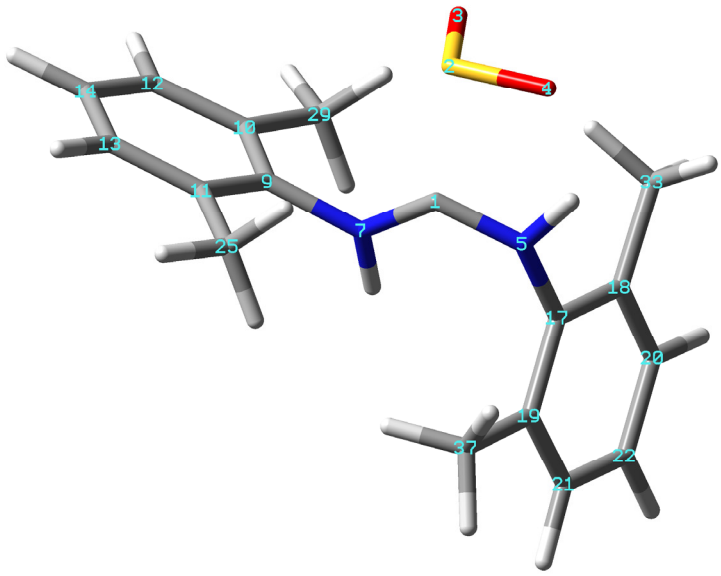


C(1)-S(2)	2.021	S(2)-C(1)-N(5)	108.649
C(1)-N(5)	1.315	S(2)-C(1)-N(7)	124.878
C(1)-N(7)	1.324	N(5)-C(1)-N(7)	124.356
S(2)-O(3)	1.504	C(1)-S(2)-O(3)	94.6080
S(2)-O(4)	1.517	C(1)-S(2)-O(4)	93.8560
N(5)-C(17)	1.436	O(3)-S(2)-O(4)	114.439
N(5)-H(6)	1.044	C(1)-N(5)-C(17)	126.760
N(7)-C(9)	1.444	C(1)-N(5)-H(6)	114.799
N(7)-H(8)	1.019	H(6)-N(5)-C(17)	118.438
C(9)-C(10)	1.405	C(1)-N(7)-C(9)	123.998
C(9)-C(11)	1.404	C(1)-N(7)-H(8)	118.367
C(10)-C(12)	1.397	H(8)-N(7)-C(9)	117.633
C(10)-C(29)	1.508	N(7)-C(9)-C(10)	118.530
C(11)-C(13)	1.399	N(7)-C(9)-C(11)	119.490
C(11)-C(25)	1.510	C(10)-C(9)-C(11)	121.964
C(12)-C(14)	1.399	C(9)-C(10)-C(12)	117.912
C(13)-C(14)	1.397	C(9)-C(10)-C(29)	120.998
C(14)-C(33)	1.510	C(12)-C(10)-C(29)	121.033
C(17)-C(18)	1.409	C(9)-C(11)-C(13)	117.832
C(17)-C(19)	1.405	C(9)-C(11)-C(25)	121.881
C(18)-C(20)	1.397	C(13)-C(11)-C(25)	120.280
C(18)-C(37)	1.511	C(10)-C(12)-C(14)	121.956
C(19)-C(21)	1.400	C(11)-C(13)-C(14)	122.007
C(19)-C(41)	1.511	C(12)-C(14)-C(13)	118.320
C(20)-C(22)	1.400	C(12)-C(14)-C(33)	120.714
C(21)-C(22)	1.397	C(13)-C(14)-C(33)	120.962
C(22)-C(45)	1.510	N(5)-C(17)-C(18)	117.968
		N(5)-C(17)-C(19)	120.130
		C(18)-C(17)-C(19)	121.900
		C(17)-C(18)-C(20)	117.788
		C(17)-C(18)-C(37)	121.126

C(20)-C(18)-C(37)	121.077
C(17)-C(19)-C(21)	117.900
C(17)-C(19)-C(41)	121.527
C(21)-C(19)-C(41)	120.564
C(18)-C(20)-C(22)	122.085
C(19)-C(21)-C(22)	121.982
C(20)-C(22)-C(21)	118.330
C(20)-C(22)-C(45)	120.644
C(21)-C(22)-C(45)	121.010

Intramolecular H-O(4) bond	1.80324 Å
Dipole moment	7.4505 D
ν_s and ν_{as} /cm^{-1}	1017, 1131
E(RB+HF-LYP) =	-1396.62807174
Zero-point correction=	0.395451 (Hartree/Particle)
Thermal correction to Energy=	0.421811
Thermal correction to Enthalpy=	0.422755
Thermal correction to Gibbs Free Energy=	0.336410
Sum of electronic and zero-point Energies=	-1396.232620
Sum of electronic and thermal Energies=	-1396.206261
Sum of electronic and thermal Enthalpies=	-1396.205316
Sum of electronic and thermal Free Energies=	-1396.291662

***N,N'*-Bis(2,6-dimethylphenyl)thiourea dioxide**

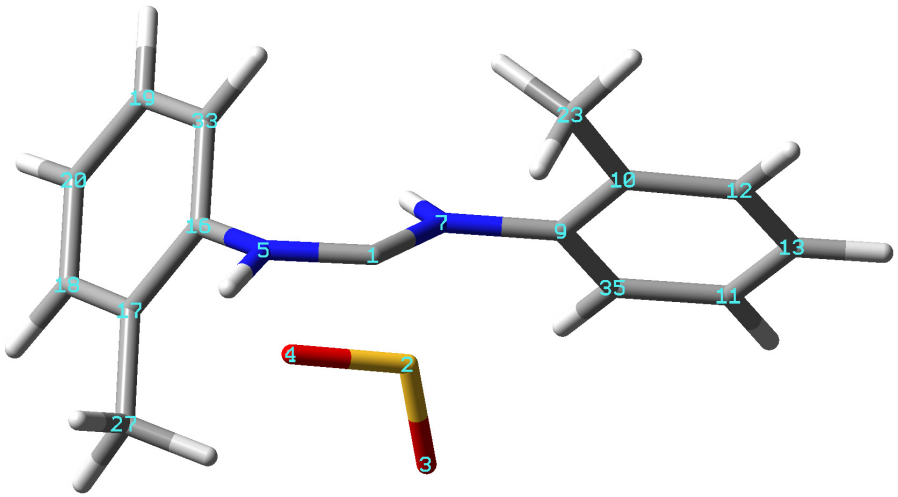


C(1)-S(2)	2.023	S(2)-C(1)-N(5)	108.569
C(1)-N(5)	1.315	S(2)-C(1)-N(7)	124.861
C(1)-N(7)	1.324	N(5)-C(1)-N(7)	124.360
S(2)-O(3)	1.504	C(1)-S(2)-O(3)	94.4300
S(2)-O(4)	1.516	C(1)-S(2)-O(4)	93.8300
N(5)-C(17)	1.436	O(3)-S(2)-O(4)	114.453
N(5)-H(6)	1.044	C(1)-N(5)-C(17)	126.632

N(7)-C(9)	1.444	C(1)-N(5)-H(6)	114.888
N(7)-H(8)	1.019	H(6)-N(5)-C(17)	118.478
C(9)-C(10)	1.406	C(1)-N(7)-C(9)	124.021
C(9)-C(11)	1.405	C(1)-N(7)-H(8)	118.490
C(10)-C(12)	1.398	H(8)-N(7)-C(9)	117.487
C(10)-C(29)	1.508	N(7)-C(9)-C(10)	118.156
C(11)-C(13)	1.400	N(7)-C(9)-C(11)	119.309
C(11)-C(25)	1.509	C(10)-C(9)-C(11)	122.509
C(12)-C(14)	1.393	C(9)-C(10)-C(12)	117.769
C(13)-C(14)	1.393	C(9)-C(10)-C(29)	121.045
C(17)-C(18)	1.409	C(12)-C(10)-C(29)	121.137
C(17)-C(19)	1.407	C(9)-C(11)-C(13)	117.667
C(18)-C(20)	1.399	C(9)-C(11)-C(25)	121.862
C(18)-C(33)	1.510	C(13)-C(11)-C(25)	120.467
C(19)-C(21)	1.400	C(10)-C(12)-C(14)	120.914
C(19)-C(37)	1.511	C(11)-C(13)-C(14)	120.976
C(20)-C(22)	1.394	C(12)-C(14)-C(13)	120.156
C(21)-C(22)	1.393	N(5)-C(17)-C(18)	117.703
		N(5)-C(17)-C(19)	119.846
		C(18)-C(17)-C(19)	122.450
		C(17)-C(18)-C(20)	117.595
		C(17)-C(18)-C(33)	121.280
		C(20)-C(18)-C(33)	121.114
		C(17)-C(19)-C(21)	117.765
		C(17)-C(19)-C(37)	121.553
		C(21)-C(19)-C(37)	120.671
		C(18)-C(20)-C(22)	121.073
		C(19)-C(21)-C(22)	120.916
		C(20)-C(22)-C(21)	120.183

Intramolecular H-O(4) bond	1.8022 Å
Dipole moment	7.0721 D
ν_s and ν_{as} /cm^{-1}	1019, 1134
E(RB+HF-LYP) =	-1317.98618417
Zero-point correction=	0.340842 (Hartree/Particle)
Thermal correction to Energy=	0.363298
Thermal correction to Enthalpy=	0.364242
Thermal correction to Gibbs Free Energy=	0.287894
Sum of electronic and zero-point Energies=	-1317.645342
Sum of electronic and thermal Energies=	-1317.622886
Sum of electronic and thermal Enthalpies=	-1317.621942
Sum of electronic and thermal Free Energies=	-1317.698290

_N,N'_-Di-_o_-tolylthiourea dioxide

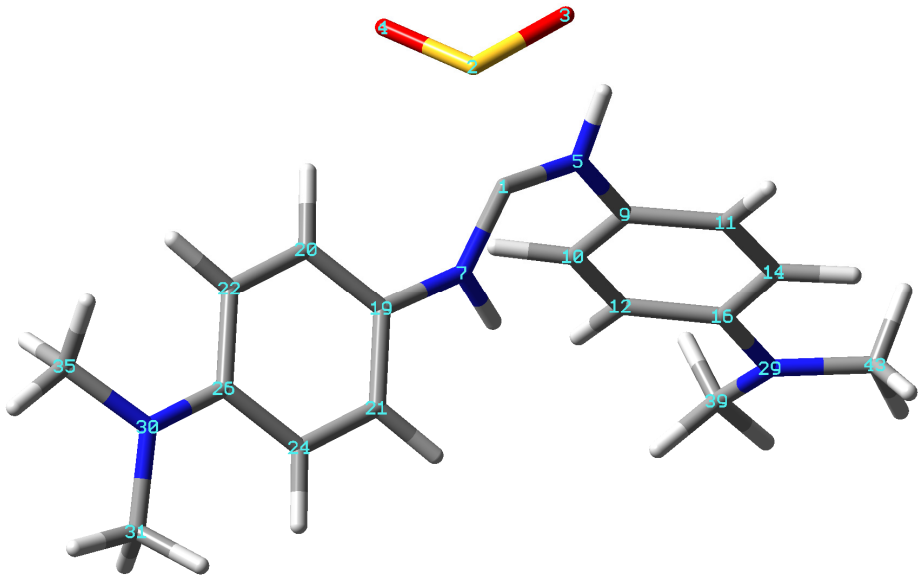


C(1)-S(2)	2.086	S(2)-C(1)-N(5)	106.474
C(1)-N(5)	1.317	S(2)-C(1)-N(7)	127.668
C(1)-N(7)	1.326	N(5)-C(1)-N(7)	123.133
S(2)-O(3)	1.494	C(1)-S(2)-O(3)	95.5640
S(2)-O(4)	1.514	C(1)-S(2)-O(4)	92.9260
N(5)-C(16)	1.428	O(3)-S(2)-O(4)	114.607
N(5)-H(6)	1.043	C(1)-N(5)-C(16)	127.923
N(7)-C(9)	1.435	C(1)-N(5)-H(6)	109.200
N(7)-H(8)	1.020	H(6)-N(5)-C(16)	120.860
C(9)-C(10)	1.407	C(1)-N(7)-C(9)	125.171
C(9)-C(35)	1.398	C(1)-N(7)-H(8)	118.312
C(10)-C(12)	1.402	H(8)-N(7)-C(9)	115.814
C(10)-C(23)	1.509	N(7)-C(9)-C(10)	121.346
C(11)-C(13)	1.395	N(7)-C(9)-C(35)	117.310
C(11)-C(35)	1.391	C(10)-C(9)-C(35)	121.270
C(12)-C(13)	1.393	C(9)-C(10)-C(12)	117.093
C(16)-C(17)	1.409	C(9)-C(10)-C(23)	122.786
C(16)-C(33)	1.398	C(12)-C(10)-C(23)	120.119
C(17)-C(18)	1.399	C(13)-C(11)-C(35)	119.422
C(17)-C(27)	1.510	C(10)-C(12)-C(13)	122.034
C(18)-C(20)	1.396	C(11)-C(13)-C(12)	119.831
C(19)-C(20)	1.394	N(5)-C(16)-C(17)	118.474
C(19)-C(33)	1.395	N(5)-C(16)-C(33)	120.054
S(2)-O(3)	1.494	C(17)-C(16)-C(33)	121.471
S(2)-O(4)	1.514	C(16)-C(17)-C(18)	117.305
		C(16)-C(17)-C(27)	120.970
		C(18)-C(17)-C(27)	121.725
		C(17)-C(18)-C(20)	121.698
		C(20)-C(19)-C(33)	119.551

C(18)-C(20)-C(19)	120.062
C(16)-C(33)-C(19)	119.910
C(9)-C(35)-C(11)	120.333
O(3)-S(2)-O(4)	114.607

Intramolecular H-O(4) bond	1.78347 Å
Dipole moment	6.9968 D
ν_s and ν_{as} /cm^{-1}	1028, 1165
E(RB+HF-LYP) =	-1239.34443047
Zero-point correction=	0.285565 (Hartree/Particle)
Thermal correction to Energy=	0.304675
Thermal correction to Enthalpy=	0.305619
Thermal correction to Gibbs Free Energy=	0.235773
Sum of electronic and zero-point Energies=	-1239.058865
Sum of electronic and thermal Energies=	-1239.039756
Sum of electronic and thermal Enthalpies=	-1239.038812
Sum of electronic and thermal Free Energies=	-1239.108658

1,3-Bis(*p*-*N,N'*-dimethylaminophenyl)thiourea dioxide

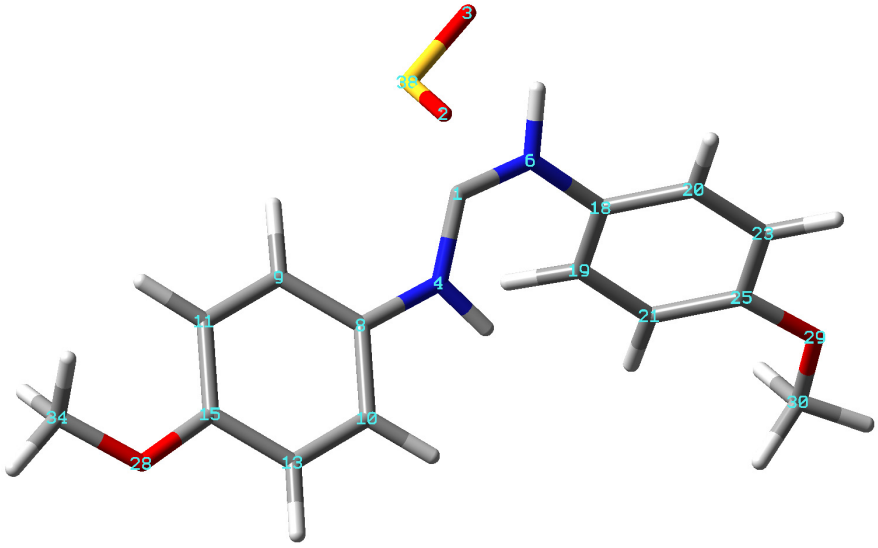


C(1)-S(2)	2.110	S(2)-C(1)-N(5)	106.789
C(1)-N(5)	1.317	S(2)-C(1)-N(7)	130.925
C(1)-N(7)	1.328	N(5)-C(1)-N(7)	122.284
S(2)-O(3)	1.515	C(1)-S(2)-O(3)	92.1500
S(2)-O(4)	1.495	C(1)-S(2)-O(4)	101.389
N(5)-C(9)	1.425	O(3)-S(2)-O(4)	114.527
N(5)-H(6)	1.043	C(1)-N(5)-C(9)	129.433
N(7)-C(19)	1.427	C(1)-N(5)-H(6)	113.781
N(7)-H(8)	1.019	H(6)-N(5)-C(9)	116.785
C(9)-C(10)	1.400	C(1)-N(7)-C(19)	127.864
C(9)-C(11)	1.398	C(1)-N(7)-H(8)	117.749
C(10)-C(12)	1.391	H(8)-N(7)-C(19)	114.385

C(11)-C(14)	1.388	N(5)-C(9)-C(10)	121.775
C(12)-C(16)	1.414	N(5)-C(9)-C(11)	119.577
C(14)-C(16)	1.416	C(10)-C(9)-C(11)	118.613
C(16)-N(29)	1.386	C(9)-C(10)-C(12)	120.799
C(19)-C(20)	1.397	C(9)-C(11)-C(14)	120.937
C(19)-C(21)	1.397	C(10)-C(12)-C(16)	121.249
C(20)-C(22)	1.390	C(11)-C(14)-C(16)	121.223
C(21)-C(24)	1.390	C(12)-C(16)-C(14)	117.148
C(22)-C(26)	1.414	C(12)-C(16)-N(29)	121.453
C(24)-C(26)	1.413	C(14)-C(16)-N(29)	121.400
C(26)-N(30)	1.389	N(7)-C(19)-C(20)	122.596
N(29)-C(39)	1.454	N(7)-C(19)-C(21)	118.263
N(29)-C(43)	1.454	C(20)-C(19)-C(21)	119.093
N(30)-C(31)	1.452	C(19)-C(20)-C(22)	120.030
N(30)-C(35)	1.453	C(19)-C(21)-C(24)	120.949
		C(20)-C(22)-C(26)	121.864
		C(21)-C(24)-C(26)	120.980
		C(22)-C(26)-C(24)	117.039
		C(22)-C(26)-N(30)	121.503
		C(24)-C(26)-N(30)	121.458
		C(16)-N(29)-C(39)	119.510
		C(16)-N(29)-C(43)	119.511
		C(39)-N(29)-C(43)	118.461
		C(26)-N(30)-C(31)	119.322
		C(26)-N(30)-C(35)	119.349
		C(31)-N(30)-C(35)	118.193

Intramolecular H-O(3) bond	1.76465 Å
Dipole moment	10.4741 D
ν_s and ν_{as} /cm^{-1}	1029, 1157
E(RB+HF-LYP) =	-1428.65576721
Zero-point correction=	0.376424 (Hartree/Particle)
Thermal correction to Energy=	0.401125
Thermal correction to Enthalpy=	0.402069
Thermal correction to Gibbs Free Energy=	0.319030
Sum of electronic and zero-point Energies=	-1428.279343
Sum of electronic and thermal Energies=	-1428.254642
Sum of electronic and thermal Enthalpies=	-1428.253698
Sum of electronic and thermal Free Energies=	-1428.336737

N,N'-Di-*p*-methoxyphenylthiourea dioxide

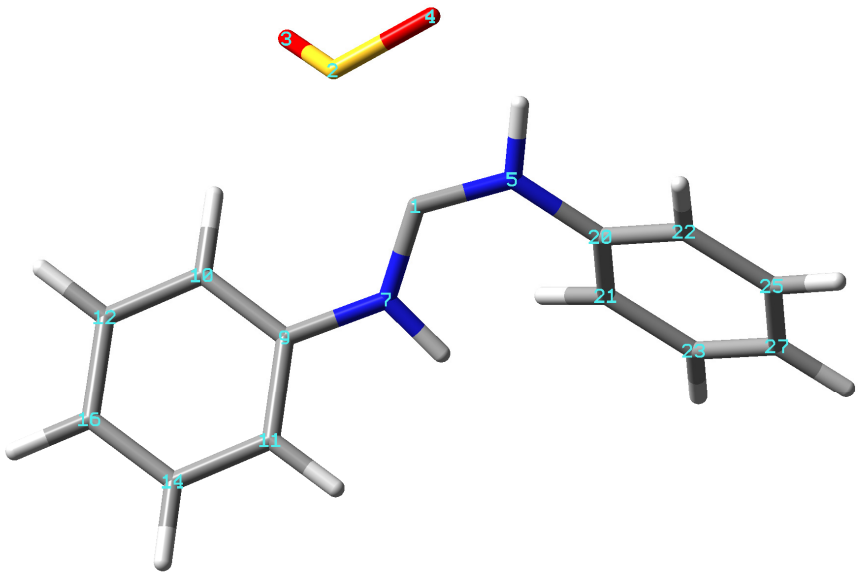


C(1)-N(4)	1.329	N(4)-C(1)-N(6)	122.235
C(1)-N(6)	1.318	N(4)-C(1)-S(38)	130.439
C(1)-S(38)	2.153	N(6)-C(1)-S(38)	105.766
O(2)-S(38)	1.487	C(1)-N(4)-C(8)	126.445
O(3)-S(38)	1.512	C(1)-N(4)-H(5)	118.265
N(4)-C(8)	1.422	H(5)-N(4)-C(8)	115.288
N(4)-H(5)	1.019	C(1)-N(6)-C(18)	129.719
N(6)-C(18)	1.425	C(1)-N(6)-H(7)	114.024
N(6)-H(7)	1.043	H(7)-N(6)-C(18)	116.255
C(8)-C(9)	1.394	N(4)-C(8)-C(9)	122.095
C(8)-C(10)	1.401	N(4)-C(8)-C(10)	118.424
C(9)-C(11)	1.395	C(9)-C(8)-C(10)	119.460
C(10)-C(13)	1.387	C(8)-C(9)-C(11)	120.306
C(11)-C(15)	1.400	C(8)-C(10)-C(13)	120.408
C(13)-C(15)	1.402	C(9)-C(11)-C(15)	120.195
C(15)-O(28)	1.364	C(10)-C(13)-C(15)	120.266
C(18)-C(19)	1.397	C(11)-C(15)-C(13)	119.349
C(18)-C(20)	1.403	C(11)-C(15)-O(28)	124.836
C(19)-C(21)	1.398	C(13)-C(15)-O(28)	115.813
C(20)-C(23)	1.386	N(6)-C(18)-C(19)	121.545
C(21)-C(25)	1.399	N(6)-C(18)-C(20)	119.086
C(23)-C(25)	1.405	C(19)-C(18)-C(20)	119.349
C(25)-O(29)	1.361	C(18)-C(19)-C(21)	120.622
O(28)-C(34)	1.420	C(18)-C(20)-C(23)	120.272
O(29)-C(30)	1.421	C(19)-C(21)-C(25)	119.780
		C(20)-C(23)-C(25)	120.414
		C(21)-C(25)-C(23)	119.551
		C(21)-C(25)-O(29)	124.814
		C(23)-C(25)-O(29)	115.634
		C(15)-O(28)-C(34)	118.186

C(25)-O(29)-C(30)	118.412
C(1)-S(38)-O(2)	98.7710
C(1)-S(38)-O(3)	91.7030
O(2)-S(38)-O(3)	115.381

Intramolecular H-O(3) bond	1.77285 Å
Dipole moment	8.5046 D
ν_s and ν_{as} /cm^{-1}	1035, 1186
E(RB+HF-LYP) =	-1389.75455111
Zero-point correction=	0.295307 (Hartree/Particle)
Thermal correction to Energy=	0.316423
Thermal correction to Enthalpy=	0.317367
Thermal correction to Gibbs Free Energy=	0.242209
Sum of electronic and zero-point Energies=	-1389.459244
Sum of electronic and thermal Energies=	-1389.438128
Sum of electronic and thermal Enthalpies=	-1389.437184
Sum of electronic and thermal Free Energies=	-1389.512342

***N,N'*-Diphenylthiourea dioxide 19**

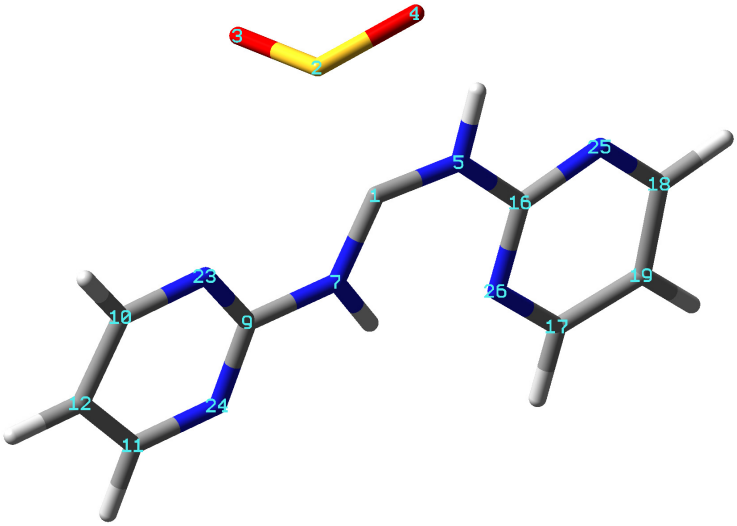


C(1)-S(2)	2.175	S(2)-C(1)-N(5)	105.326
C(1)-N(5)	1.318	S(2)-C(1)-N(7)	132.593
C(1)-N(7)	1.330	N(5)-C(1)-N(7)	122.076
S(2)-O(3)	1.490	C(1)-S(2)-O(3)	101.824
S(2)-O(4)	1.511	C(1)-S(2)-O(4)	91.2260
N(5)-C(20)	1.424	O(3)-S(2)-O(4)	114.814
N(5)-H(6)	1.043	C(1)-N(5)-C(20)	130.232
N(7)-C(9)	1.425	C(1)-N(5)-H(6)	113.876
N(7)-H(8)	1.019	H(6)-N(5)-C(20)	115.891
C(9)-C(10)	1.398	C(1)-N(7)-C(9)	127.234
C(9)-C(11)	1.399	C(1)-N(7)-H(8)	118.181
C(10)-C(12)	1.395	H(8)-N(7)-C(9)	114.583
C(11)-C(14)	1.393	N(7)-C(9)-C(10)	121.921

C(12)-C(16)	1.396	N(7)-C(9)-C(11)	117.572
C(14)-C(16)	1.396	C(10)-C(9)-C(11)	120.480
C(20)-C(21)	1.401	C(9)-C(10)-C(12)	118.959
C(20)-C(22)	1.400	C(9)-C(11)-C(14)	119.847
C(21)-C(23)	1.396	C(10)-C(12)-C(16)	121.000
C(22)-C(25)	1.393	C(11)-C(14)-C(16)	120.166
C(23)-C(27)	1.395	C(12)-C(16)-C(14)	119.532
C(25)-C(27)	1.397	N(5)-C(20)-C(21)	121.269
		N(5)-C(20)-C(22)	118.642
		C(21)-C(20)-C(22)	120.071
		C(20)-C(21)-C(23)	119.635
		C(20)-C(22)-C(25)	119.791
		C(21)-C(23)-C(27)	120.399
		C(22)-C(25)-C(27)	120.355
		C(23)-C(27)-C(25)	119.735

Intramolecular H-O(4) bond	1.75301 Å
Dipole moment	7.9972 D
ν_s and ν_{as} /cm^{-1}	1033, 1177
E(RB+HF-LYP) =	-1160.70703443
Zero-point correction=	0.230297 (Hartree/Particle)
Thermal correction to Energy=	0.246114
Thermal correction to Enthalpy=	0.247059
Thermal correction to Gibbs Free Energy=	0.184494
Sum of electronic and zero-point Energies=	-1160.476738
Sum of electronic and thermal Energies=	-1160.460920
Sum of electronic and thermal Enthalpies=	-1160.459976
Sum of electronic and thermal Free Energies=	-1160.522540

_N,N'_-Di(2-pyrimidinyl)thiourea dioxide

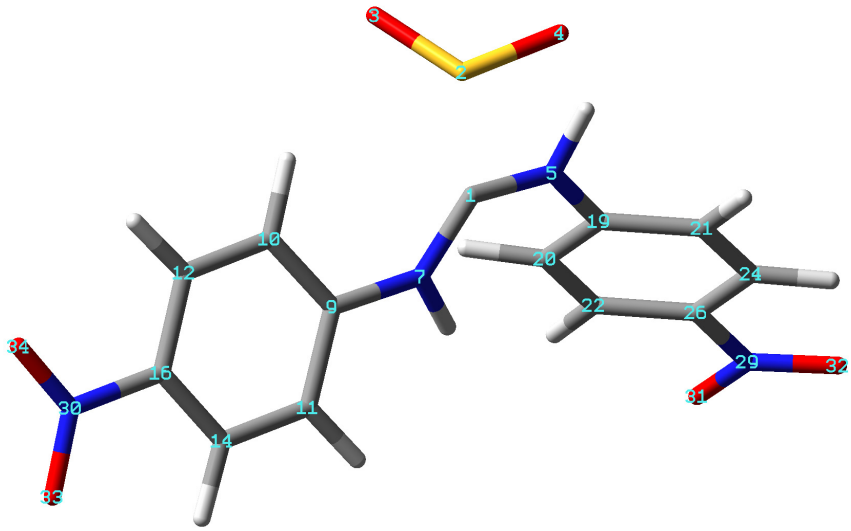


C(1)-S(2)	2.202	S(2)-C(1)-N(5)	104.850
C(1)-N(5)	1.328	S(2)-C(1)-N(7)	132.668
C(1)-N(7)	1.328	N(5)-C(1)-N(7)	121.311
S(2)-O(3)	1.485	C(1)-S(2)-O(3)	98.7480

S(2)-O(4)	1.510	C(1)-S(2)-O(4)	90.6360
N(5)-C(16)	1.396	O(3)-S(2)-O(4)	114.951
N(5)-H(6)	1.045	C(1)-N(5)-C(16)	131.800
N(7)-C(9)	1.406	C(1)-N(5)-H(6)	114.319
N(7)-H(8)	1.025	H(6)-N(5)-C(16)	113.880
C(9)-N(23)	1.332	C(1)-N(7)-C(9)	124.974
C(9)-N(24)	1.337	C(1)-N(7)-H(8)	118.633
C(10)-C(12)	1.394	H(8)-N(7)-C(9)	116.391
C(10)-N(23)	1.335	N(7)-C(9)-N(23)	118.337
C(11)-C(12)	1.393	N(7)-C(9)-N(24)	113.832
C(11)-N(24)	1.337	N(23)-C(9)-N(24)	127.828
C(16)-N(25)	1.339	C(12)-C(10)-N(23)	122.519
C(16)-N(26)	1.341	C(12)-C(11)-N(24)	122.494
C(17)-C(19)	1.390	C(10)-C(12)-C(11)	116.271
C(17)-N(26)	1.339	N(5)-C(16)-N(25)	114.935
C(18)-C(19)	1.397	N(5)-C(16)-N(26)	118.193
C(18)-N(25)	1.333	N(25)-C(16)-N(26)	126.872
		C(19)-C(17)-N(26)	122.315
		C(19)-C(18)-N(25)	122.667
		C(17)-C(19)-C(18)	116.297
		C(9)-N(23)-C(10)	115.507
		C(9)-N(24)-C(11)	115.362
		C(16)-N(25)-C(18)	115.836
		C(16)-N(26)-C(17)	116.013

Intramolecular H-O(4) bond	1.77668 Å
Dipole moment	8.9799 D
ν_s and ν_{as} /cm^{-1}	1041, 1192
E(RB+HF-LYP) =	-1224.87560101
Zero-point correction=	0.183495 (Hartree/Particle)
Thermal correction to Energy=	0.198617
Thermal correction to Enthalpy=	0.199561
Thermal correction to Gibbs Free Energy=	0.138481
Sum of electronic and zero-point Energies=	-1224.692106
Sum of electronic and thermal Energies=	-1224.676985
Sum of electronic and thermal Enthalpies=	-1224.676040
Sum of electronic and thermal Free Energies=	-1224.737120

N,N'-Di-*p*-nitrophenylthiourea dioxide

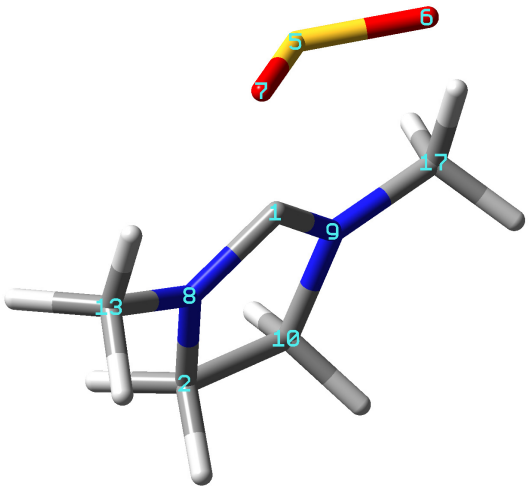


C(1)-S(2)	2.280	S(2)-C(1)-N(5)	103.411
C(1)-N(5)	1.321	S(2)-C(1)-N(7)	135.038
C(1)-N(7)	1.334	N(5)-C(1)-N(7)	121.457
S(2)-O(3)	1.483	C(1)-S(2)-O(3)	102.549
S(2)-O(4)	1.504	C(1)-S(2)-O(4)	89.8380
N(5)-C(19)	1.419	O(3)-S(2)-O(4)	115.408
N(5)-H(6)	1.042	C(1)-N(5)-C(19)	131.320
N(7)-C(9)	1.418	C(1)-N(5)-H(6)	113.987
N(7)-H(8)	1.020	H(6)-N(5)-C(19)	114.691
C(9)-C(10)	1.401	C(1)-N(7)-C(9)	126.175
C(9)-C(11)	1.402	C(1)-N(7)-H(8)	118.774
C(10)-C(12)	1.390	H(8)-N(7)-C(9)	115.049
C(11)-C(14)	1.389	N(7)-C(9)-C(10)	121.779
C(12)-C(16)	1.394	N(7)-C(9)-C(11)	117.625
C(14)-C(16)	1.393	C(10)-C(9)-C(11)	120.574
C(16)-N(30)	1.469	C(9)-C(10)-C(12)	119.270
C(19)-C(20)	1.404	C(9)-C(11)-C(14)	120.134
C(19)-C(21)	1.403	C(10)-C(12)-C(16)	119.509
C(20)-C(22)	1.392	C(11)-C(14)-C(16)	118.730
C(21)-C(24)	1.389	C(12)-C(16)-C(14)	121.770
C(22)-C(26)	1.392	C(12)-C(16)-N(30)	119.282
C(24)-C(26)	1.394	C(14)-C(16)-N(30)	118.946
C(26)-N(29)	1.472	N(5)-C(19)-C(20)	121.606
N(29)-O(31)	1.230	N(5)-C(19)-C(21)	118.218
N(29)-O(32)	1.229	C(20)-C(19)-C(21)	120.152
N(30)-O(33)	1.231	C(19)-C(20)-C(22)	119.890
N(30)-O(34)	1.230	C(19)-C(21)-C(24)	120.121
		C(20)-C(22)-C(26)	118.974
		C(21)-C(24)-C(26)	118.851
		C(22)-C(26)-C(24)	121.989

C(22)-C(26)-N(29)	118.961
C(24)-C(26)-N(29)	119.047
C(26)-N(29)-O(31)	117.461
C(26)-N(29)-O(32)	117.463
O(31)-N(29)-O(32)	125.076
C(16)-N(30)-O(33)	117.534
C(16)-N(30)-O(34)	117.622
O(33)-N(30)-O(34)	124.843

Intramolecular H-O(4) bond	1.75243 Å
Dipole moment	4.3502 D
ν_s and ν_{as} /cm^{-1}	1048, 1210
E(RB+HF-LYP) =	-1569.70106205
Zero-point correction=	0.235030 (Hartree/Particle)
Thermal correction to Energy=	0.256067
Thermal correction to Enthalpy=	0.257011
Thermal correction to Gibbs Free Energy=	0.180695
Sum of electronic and zero-point Energies=	-1569.466032
Sum of electronic and thermal Energies=	-1569.444995
Sum of electronic and thermal Enthalpies=	-1569.444051
Sum of electronic and thermal Free Energies=	-1569.520367

_N,N'_-Dimethylethylenethiourea dioxide 61

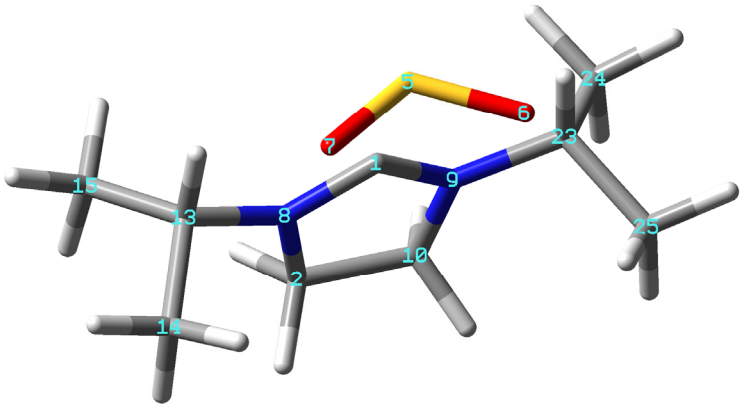


C(1)-S(5)	2.293	S(5)-C(1)-N(8)	124.793
C(1)-N(8)	1.333	S(5)-C(1)-N(9)	124.767
C(1)-N(9)	1.333	N(8)-C(1)-N(9)	109.43
C(2)-N(8)	1.478	N(8)-C(2)-C(10)	102.396
C(2)-C(10)	1.542	C(1)-S(5)-O(6)	99.881
S(5)-O(6)	1.487	C(1)-S(5)-O(7)	99.873
S(5)-O(7)	1.487	O(6)-S(5)-O(7)	115.666
N(8)-C(13)	1.453	C(1)-N(8)-C(2)	112.888
N(9)-C(10)	1.478	C(1)-N(8)-C(13)	126.312
N(9)-C(17)	1.453	C(2)-N(8)-C(13)	120.779
		C(1)-N(9)-C(10)	112.886

C(1)-N(9)-C(17)	126.292
C(10)-N(9)-C(17)	120.778
C(2)-C(10)-N(9)	102.395

Dipole moment	8.2606 D
ν_s and ν_{as} /cm^{-1}	1085, 1231
E(RB+HF-LYP) =	-854.626753563
Zero-point correction=	0.159725 (Hartree/Particle)
Thermal correction to Energy=	0.171522
Thermal correction to Enthalpy=	0.172466
Thermal correction to Gibbs Free Energy=	0.119988
Sum of electronic and zero-point Energies=	-854.467029
Sum of electronic and thermal Energies=	-854.455232
Sum of electronic and thermal Enthalpies=	-854.454287
Sum of electronic and thermal Free Energies=	-854.506766

_N,N'_-Diisopropylethylenethiourea dioxide 62

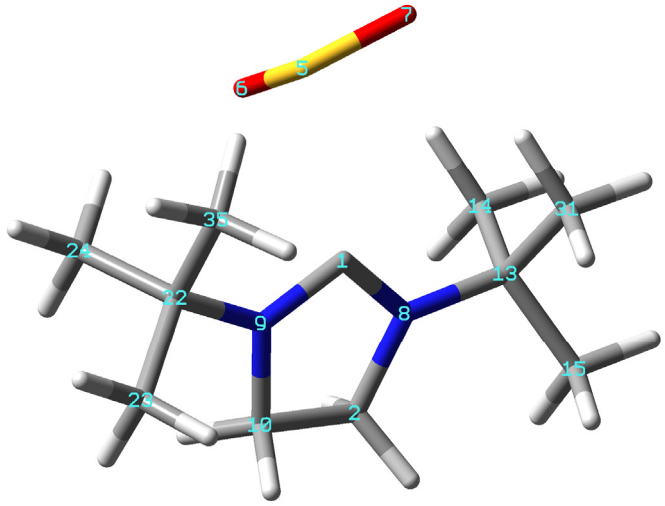


C(1)-S(5)	2.304	S(5)-C(1)-N(8)	124.768
C(1)-N(8)	1.334	S(5)-C(1)-N(9)	124.238
C(1)-N(9)	1.334	N(8)-C(1)-N(9)	110.181
C(2)-N(8)	1.481	N(8)-C(2)-C(10)	102.599
C(2)-C(10)	1.543	C(1)-S(5)-O(6)	97.85
S(5)-O(6)	1.489	C(1)-S(5)-O(7)	97.971
S(5)-O(7)	1.489	O(6)-S(5)-O(7)	115.31
N(8)-C(13)	1.475	C(1)-N(8)-C(2)	112.297
N(9)-C(10)	1.482	C(1)-N(8)-C(13)	125.313
N(9)-C(23)	1.475	C(2)-N(8)-C(13)	122.302
C(13)-C(14)	1.533	C(1)-N(9)-C(10)	112.281
C(13)-C(15)	1.533	C(1)-N(9)-C(23)	125.27
C(23)-C(24)	1.533	C(10)-N(9)-C(23)	122.287
C(23)-C(25)	1.533	C(2)-C(10)-N(9)	102.571
		N(8)-C(13)-C(14)	111.14
		N(8)-C(13)-C(15)	110.887
		C(14)-C(13)-C(15)	112.659
		N(9)-C(23)-C(24)	110.86

N(9)-C(23)-C(25)	111.21
C(24)-C(23)-C(25)	112.694

Dipole moment	7.4188 D
ν_s and ν_{as} /cm^{-1}	1078, 1225
E(RB+HF-LYP) =	-1011.89998432
Zero-point correction=	0.272818 (Hartree/Particle)
Thermal correction to Energy=	0.290098
Thermal correction to Enthalpy=	0.291043
Thermal correction to Gibbs Free Energy=	0.224743
Sum of electronic and zero-point Energies=	-1011.627166
Sum of electronic and thermal Energies=	-1011.609886
Sum of electronic and thermal Enthalpies=	-1011.608942
Sum of electronic and thermal Free Energies=	-1011.675242

_N,N'_-Di-_tert_-butylethylenethiourea dioxide 9



C(1)-S(5)	2.488	S(5)-C(1)-N(8)	121.955
C(1)-N(8)	1.343	S(5)-C(1)-N(9)	116.165
C(1)-N(9)	1.344	N(8)-C(1)-N(9)	109.153
C(2)-N(8)	1.482	N(8)-C(2)-C(10)	102.601
C(2)-C(10)	1.533	C(1)-S(5)-O(6)	91.6330
S(5)-O(6)	1.483	C(1)-S(5)-O(7)	105.990
S(5)-O(7)	1.481	O(6)-S(5)-O(7)	115.443
N(8)-C(13)	1.494	C(1)-N(8)-C(2)	112.097
N(9)-C(10)	1.482	C(1)-N(8)-C(13)	126.277
N(9)-C(22)	1.490	C(2)-N(8)-C(13)	121.152
C(13)-C(14)	1.541	C(1)-N(9)-C(10)	112.407
C(13)-C(15)	1.541	C(1)-N(9)-C(22)	127.149
C(13)-C(31)	1.537	C(10)-N(9)-C(22)	120.411
C(22)-C(23)	1.543	C(2)-C(10)-N(9)	102.631
C(22)-C(24)	1.542	N(8)-C(13)-C(14)	109.961
C(22)-C(35)	1.537	N(8)-C(13)-C(15)	108.842
		N(8)-C(13)-C(31)	109.058
		C(14)-C(13)-C(15)	109.343

C(14)-C(13)-C(31)	111.446
C(15)-C(13)-C(31)	108.134
N(9)-C(22)-C(23)	108.930
N(9)-C(22)-C(24)	109.421
N(9)-C(22)-C(35)	110.129
C(23)-C(22)-C(24)	109.458
C(23)-C(22)-C(35)	107.786
C(24)-C(22)-C(35)	111.074

Dipole moment	6.2053 D
ν_s and ν_{as} /cm^{-1}	1092, 1251
E(RB+HF-LYP) =	-1090.52148646
Zero-point correction=	0.328624 (Hartree/Particle)
Thermal correction to Energy=	0.347992
Thermal correction to Enthalpy=	0.348936
Thermal correction to Gibbs Free Energy=	0.282073
Sum of electronic and zero-point Energies=	-1090.192862
Sum of electronic and thermal Energies=	-1090.173494
Sum of electronic and thermal Enthalpies=	-1090.172550
Sum of electronic and thermal Free Energies=	-1090.239413