Novel Mediators For Oxidation Using Hydrogen Peroxide

Thesis Submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy

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Abbreviations Used In The Text:

acac	Acetylacetonate
Acc	Accurate mass
DBU	1,8-diazabicyclo[5.4.0.]undec-7-ene
DCM	Dichloromethane
EDTA	Ethylenediaminetetraacetic acid
EI	Electron ionisation
eq	Equivalents
FAB	Fast atom bombardment
HEDTRA	*N*-(2-Hydroxyethyl)ethylenediaminetriacetic acid
HMPT	Hexamethylphosphorous triamide
HPLC	High performance liquid chromatography
*m*CPBA	*meta*-Chloroperbenzoic acid
mp	Melting point
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
PDTA	3-(2-Pyridyl)-5,6-diphenyl-1,2,4-triazine
Phth	phthaloyl
SAS	Statistical Analysis System
SPC	Sodium percarbonate
TLC	Thin layer chromatography
UHP	Urea hydrogen peroxide
UV	Ultra violet

Abstract

This thesis is aimed at the discovery and development of novel mediators for the rapid transfer of oxygen from hydrogen peroxide to selected sulfides. The electrophilic oxidation of sulfides to sulfoxides is taken as a model reaction representing the oxidation of stain molecules.

The thesis is divided into seven chapters. The first chapter is an introduction to domestic cleaning, stains and the bleaches used for soil removal. There is a brief review of *O*-based bleaches and a description of why electrophilic oxidants are useful in this area. The second chapter is concerned with the many different compounds used to activate the environmentally friendly oxidant hydrogen peroxide towards the oxidation of sulfides. Many of these oxidations are directed towards the synthesis of chiral sulfoxides because of their importance in organic synthesis. An outline of the present investigation is then given.

The third chapter outlines the synthesis of a range of iminium salts based on the benzoxazolium, benzothiazolium and benzimidazolium structures. The fourth chapter is concerned with the evaluation of these iminium salts as mediators for the oxidation of thioanisole with sodium percarbonate as the oxidant (providing a constant, low concentration of hydrogen peroxide). Also assessed are *N*-methyl-3, 4-dihydroisoquinolinium tetrafluoroborate and 3-*t*-butyl-1, 2-benzisothiazole-1,1-dioxide, which have been previously developed for use as *O*-transfer agents. The benzoxazolium salts are shown to be most effective at 40°C, with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate **(41)** giving 70 % conversion of thioanisole in 24 hours. At 25°C, **(41)** gives almost complete conversion of thioanisole when present in equimolar quantities.

The mechanism of the oxidation is then investigated in the fifth chapter by assessing the effect of the initial concentrations of the components upon the rate of reaction. A possible reaction mechanism is proposed and the data is fitted to an integrated rate equation. Some of the mediators are also assessed under homogeneous reaction conditions in a set of competitive oxidations of 4-substituted thioanisoles.

In the sixth chapter some iminium salts are assessed as activators of hydrogen peroxide in hard surface cleaning applications. The appraisal involves monitoring the

ability of these systems to remove two types of model soil: curcumin-oil on formica tiles and mould paste on unglazed kitchen tiles.

The seventh chapter describes the experimental procedures in detail; also included in this section is the derivation of any equations used in the thesis.

Contents

Acknowledgements ii
Abbreviations iii
Abstract iv
Contents vi

Chapter 1: Introduction

1.1 Introduction 2

1.2 Cleaning 2

1.3 Types of stain and soil 3
1.3.1 Stain removal 5

1.4 Oxygen-based bleaches 5
1.4.1 Sodium hypochlorite [sodium oxochlorate (I)] 6
1.4.2 Hydrogen peroxide 7
1.4.3 Oxone® **(12)** 12
1.4.4 Molecular oxygen/ air 13
1.4.5 Ozone 14

1.5 Electrophilic oxidants 15

Chapter 2: The environmentally-friendly oxidation of sulfides to sulfoxides

2.1 Introduction 20

2.2 Hydrogen peroxide 21

2.3 Activation of hydrogen peroxide 22
2.3.1 Acids 22
2.3.2 The '*in situ*' generation of peracids 23
2.3.3 Transition metals 25
2.3.4 The generation of organic hydroperoxides 32

2.4 Other oxidants 34
2.4.1 Oxaziridines 35
2.4.2 Oxaziridinium salts 36

2.5 Novel activators of hydrogen peroxide 38

2.6 Conclusions 46

2.7 The present investigation 48

Chapter 3: Synthesis of iminium salts

3.1 Introduction 56

3.2 Synthesis of benzoxazolium and benzothiazolium salts 57
3.2.1 Preparation of benzoxazoles 57
3.2.2 Preparation of benzothiazoles 58
3.2.3 *N*-Methylation by methyl tosylate 59
3.2.4 *N*-Methylation by Meerwein's reagent 59

3.3 Synthesis of benzimidazolium salts 61
3.3.1 1, 3-Dimethyl-2-*t*-butylbenzimidazolium tetrafluoroborate **(42)** 61
3.3.2 1, 3-Dimethyl-2-phenylbenzimidazolium tosylate **(43)** 61

3.4 Synthesis of 1,2,3,3-tetramethylindoleninium tetrafluoroborate **(44)** 62

Chapter 4: The use of iminium salts for the oxidation of thioanisole

4.1 The use of benzoxazolium mediators for the oxidation of thioanisole 65
4.1.1 3-Methylbenzoxazolium tetrafluoroborate **(35)** 67
4.1.2 2,3-Dimethylbenzoxazolium tosylate **(47)** 68
4.1.3 2-Chloro-3-ethylbenzoxazolium tetrafluoroborate **(41)** 69
4.1.4 2-Phenyl-3-methylbenzoxazolium tetrafluoroborate **(36)** 69
4.1.5 2-*tert*-Butyl-3-methylbenzoxazolium tetrafluoroborate **(37)** 70
4.1.6 Discussion 71
4.1.7 *N*-Methyl-3, 4-dihydroisoquinolinium tosylate **(54)** 75

4.2 The use of benzothiazolium mediators for the oxidation of thioanisole 76
4.2.1 3-Methylbenzothiazolium tetrafluoroborate **(38)** 78
4.2.2 2,3-Dimethylbenzothiazolium tosylate **(58)** 79
4.2.3 2-Phenyl-3-methylbenzothiazolium tetrafluoroborate **(39)** 80
4.2.4 2-*tert*-Butyl-3-methylbenzothiazolium tetrafluoroborate **(40)** 81

4.3 The use of other mediators for the oxidation of thioanisole 81
4.3.1 1, 3-Dimethyl-2-*t*-butylbenzimidazolium tetrafluoroborate **(42)** 82
4.3.2 1, 3-Dimethyl-2-phenylbenzimidazolium tetrafluoroborate **(43)** 82
4.3.3 1,2,3,3-Tetramethyl-3*H*-indoleninium tetrafluoroborate **(44)** 83
4.3.4 3-*t*-Butyl-1, 2-benzisothiazole-1,1-dioxide (65) 84

4.4 Heterogeneous oxidation at a higher temperature 85
4.4.1 Discussion 86

Chapter 5: Investigation of the mechanism of oxidation

5.1	Investigation of the heterogeneous reactions	91
5.1.1	Uncatalysed reactions	92
5.1.2	Interpretation of rate laws for the mediated oxidations	92
5.1.3	2-*t*-Butyl-3-methylbenzoxazolium tetrafluoroborate **(37)**	95
5.1.4	2-Phenyl-3-methylbenzoxazolium tetrafluoroborate **(36)**	97
5.1.5	2-Chloro-3-ethylbenzoxazolium tetrafluoroborate **(41)**	100
5.1.6	3-Methylbenzoxazolium tetrafluoroborate **(35)**	103
5.1.7	2-Methyl-3,4-dihydroisoquinolinium tosylate **(54)**	105
5.1.8	Conclusions	107
5.2	Competitive oxidation of substituted thioanisoles	110
5.2.1	Introduction to structure-activity relationships	110
5.2.2	Choice of substituent constant	111
5.2.3	Assessment of substituent effects	111
5.2.4	Uncatalysed oxidations	112
5.2.5	3-Methylbenzoxazolium tetrafluoroborate **(35)**	113
5.2.6	2-Chloro-3-ethylbenzoxazolium tetrafluoroborate **(41)**	114
5.2.7	2-Phenyl-3-methylbenzoxazolium tetrafluoroborate **(36)**	115
5.2.8	2-*t*-Butyl-3-methylbenzoxazolium tetrafluoroborate **(37)**	116
5.2.9	3-*tert*-Butyl-1,2-benzisothiazole 1,1-dioxide **(65)**	117
5.2.10	Conclusions	118
5.3	Mechanistic Interpretation	122
5.3.1	2-Alkyl- and 2-aryl-benzoxazolium salts	122
5.3.2	2-Chloro-3-ethyl-benzoxazolium tetrafluoroborate	123
5.4	Conclusions	126

Chapter 6: The use of iminium salts for hard surface cleaning applications

6.1	Introduction	132
6.2	Bleaching of curcumin-oil on formica tiles	133
6.2.1	Preparation of stain model	133
6.2.2	Preparation of bleaching systems	133
6.2.3	Procedure for stain removal	134
6.2.4	Assessment of soil removal	134
6.2.5	Results	135
6.2.6	Conclusions	139
6.3	Mould paste on unglazed ceramic tiles	140
6.3.1	Preparation of mould paste	140
6.3.2	Preparation of tiles	140
6.3.3	Procedure for stain removal	140
6.3.4	Assessment of soil removal	140

6.3.5 Results 140
6.3.6 Conclusions 144

6.4 Conclusions 145

Chapter 7:Experimental Section

7.1 Instrumentation and experimental techniques 149
7.2 General procedures for the oxidation of sulfides 150
7.3 HPLC analysis 151
7.4 Preparation of sulfide reactants and sulfoxide products 152
7.5 Preparation of *O*-transfer mediators and their precursors 154
7.6 Products arising from the decomposition of the mediators 164
7.7 Derivation of equations 172
7.8 Calculation of experimental error 173

Chapter 1

Introduction

1.1 Introduction

The oxidation of organic compounds is a very important process both industrially and academically; indeed both areas approach catalytic oxidation in the same way, aiming to develop selectivity in conjunction with clean technology. In organic synthesis, selective oxidation is fundamental since it is often necessary to oxidise a particular functional group within a molecule, without over-oxidation and without affecting other potentially oxidisable groups. Perhaps the most sensitive test of the selectivity of a reagent is stereoselectivity, particularly enantioselectivity.

Selective oxidation in the cleaning industry is important because, for example, dirt particles and stains need to be removed from clothes without damaging fabric or dyes. The perfect oxygen-based bleaching agent would oxidise stains at low temperatures, but not clothes nor their dyes. Thus to develop a good bleaching agent, it is important to understand the nature of stains.

The aim of this project was the discovery and development of novel compounds for the transfer of oxygen from the environmentally friendly oxidant hydrogen peroxide to selected organic molecules, chosen to model common classes of household stains.

This chapter will give a brief introduction to household cleaning and the removal of stains. Also discussed are oxygen-based bleaches and electrophilic oxidants, which are used for stain removal.

1.2 Cleaning

In household cleaning, stain removal is the number one unmet consumer need. The removal of soils is achieved by physical-mechanical methods (for loose dirt) and by the breakdown of staining pigments into simpler components by oxidation of their chromophoric systems. Domestic cleaning can be divided into two main areas: hard surface cleaning and laundry.

Features of hard surface cleaning include a high loading of complex, multi-component soils and a high bleach and surfactant concentration if used neat (although the product may be diluted in use). Due to customer requirements hard surface cleaning takes place at ambient temperatures, features relatively short contact times and a low to medium mechanical energy input (wiping). Fabric bleaching, which usually takes place in a washing machine, typically features low soil loadings and a

low product concentration; contact times are longer and there is generally a warm wash liquor (time and temperature are controlled by the consumer) and agitation by machine or by hand to aid soil removal. In both cases the level and type of bleach is controlled by the detergent manufacturer.

1.3 Types of stain and soil

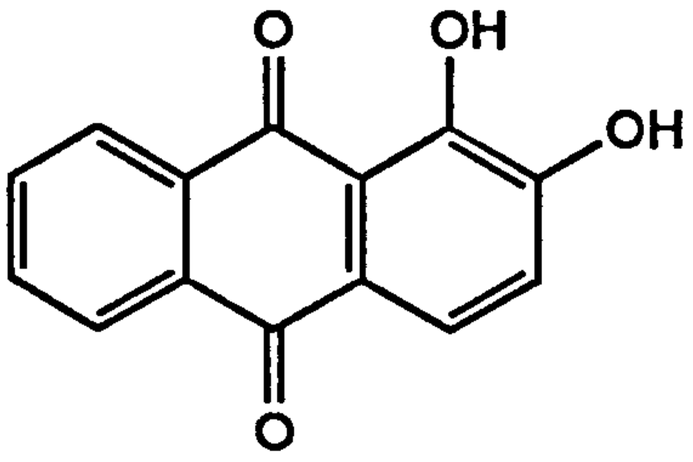
Stains are localised concentrations of unwanted coloured material on a fabric or surface. They are usually accidental in origin and include a wide range of materials: tea, wine, fruit-juices, food sauces such as curry and bolognaise, cosmetics such as lipstick and mascara, biro ink and other writing materials, plant derived stains such as grass and banana sap, body stains such as blood, faeces, collar and cuff soil, shoe polishes, motor oil and rust. Furthermore pyrolytic, photolytic, aerobic ageing of the stain often reduces the ease of removal.

Stain molecules are either hydrophobic or hydrophilic. Hydrophobic stains include chlorophyllins (e.g. grass stains) which possess a long hydrocarbon chain and repel water. The anthocyanins present in red wine and fruit juices are examples of hydrophilic stains.

Typical representatives of household stains are quinones, carotenoids and polyphenolics. Hydroxyanthraquinones can be found in fungi, plants and invertebrates and more than forty pigments based on this structure are known; furthermore, hydroxyanthraquinones have been used for many years as dying agents [e.g. cochineal, alizarin **(1)**]. Carotenoids are present in plant (carrots, tomatoes) and animal pigments and, as such, occur in many foodstuffs [e.g. β-carotene **(3)**, lycopene, crocetin]; they are also added artificially to some foods e.g. margarine. Complex polyphenols are said to be the commonest stain species found on domestic laundry[1, 2] and include flavone **(2)** derivatives (flavonoids) found in red wine and the anthocyanins **(4)** present in tea. In the WC stains are of variable composition and dependant upon diet, health etc. Stains typically consist of a mixture of food remnants: a combination of protein, cellulose, carbohydrates, fats and high levels of bacteria.

Mechanistic investigations into the oxidation of natural pigments are made easier by the use of less complex representatives, containing similar functionality whilst being available in a chemically pure form. By studying the oxidation of organic

compounds in solution one can investigate the removal of soils due to chromophore destruction. For example, previous groups have studied the oxidation of chrysin **(5)**, eosin **(6)** and phenolphthalein **(7)**.[3]



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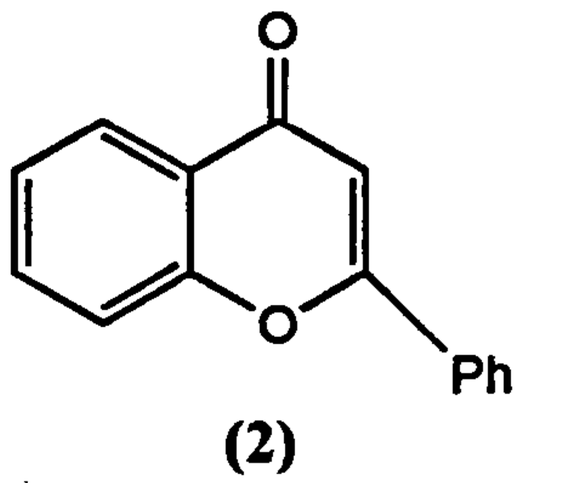

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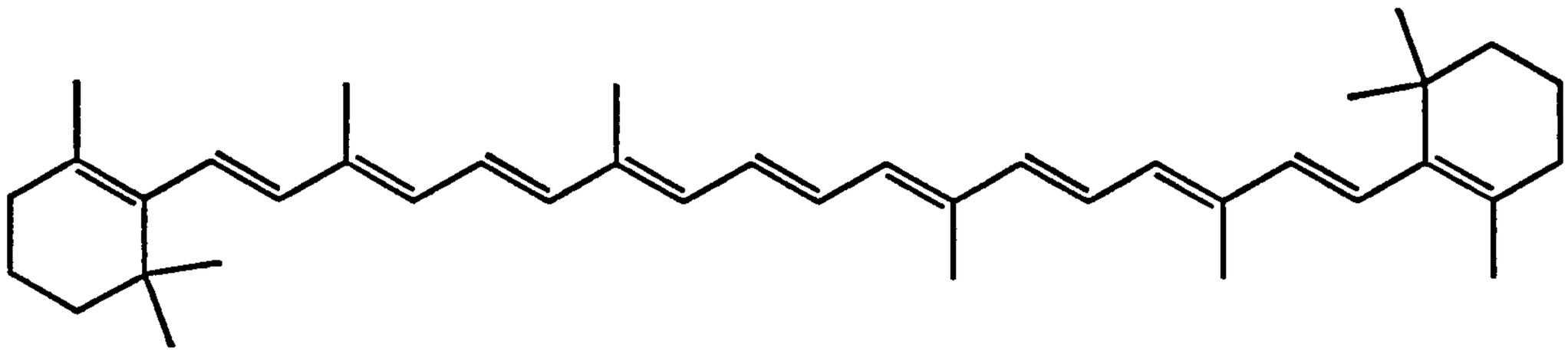

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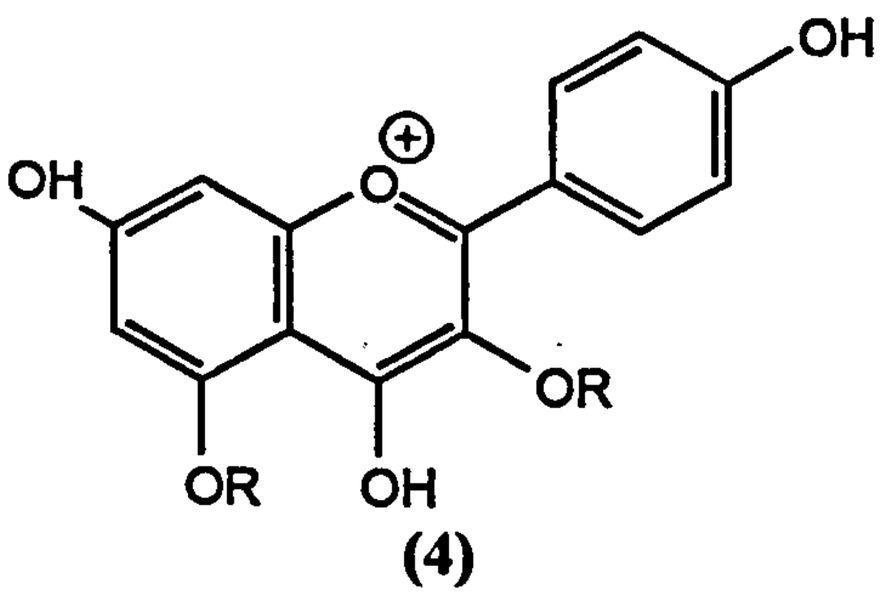

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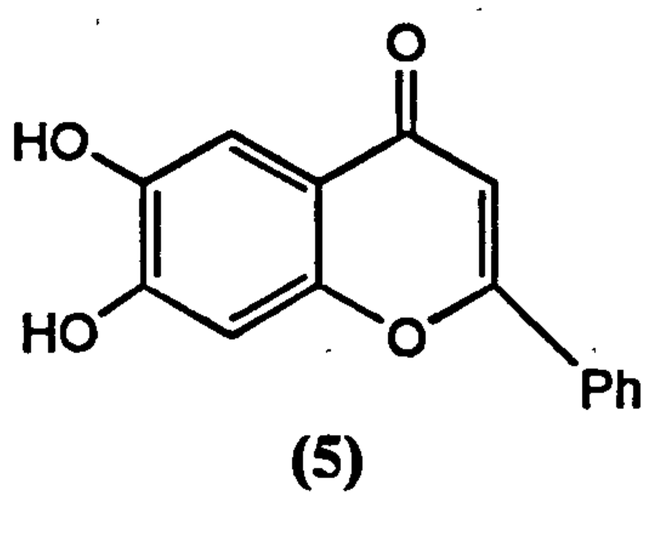

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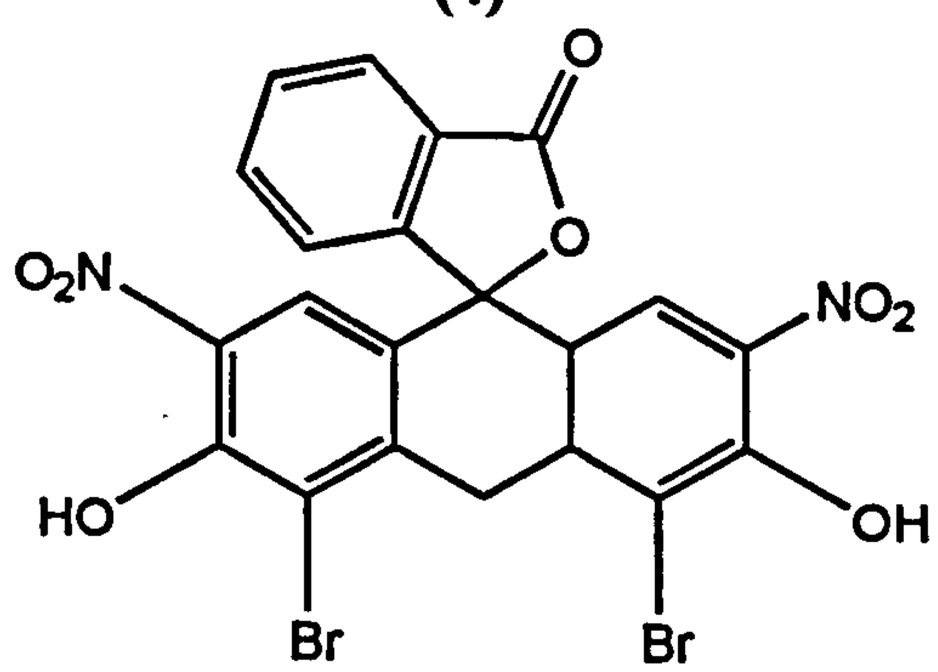

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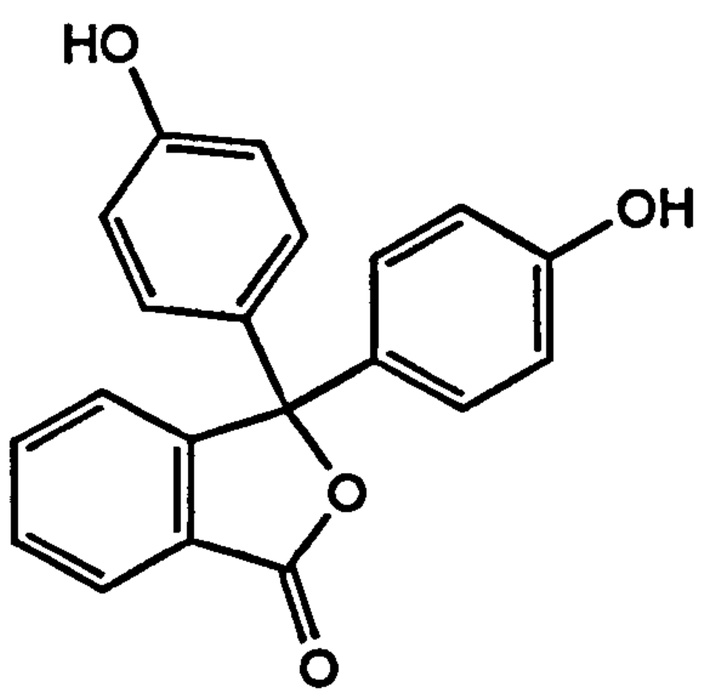


(7)

The exact nature of the chromophoric materials present in residual stains is difficult to determine because the concentrations of stain chromophores are often too low to detect above the background levels of the textile by spectroscopic methods.

1.3.1 Stain removal

Good stain removal is an important performance attribute of laundry products and hard surface cleaners. The colours in stains are caused by the presence of extended conjugation within the molecules. Stains are removed by the oxidative, irreversible destruction or modification of their chromophoric systems and their breakdown into simpler, more water-soluble molecules. The problem of stain removal varies considerably depending upon the type of stain.

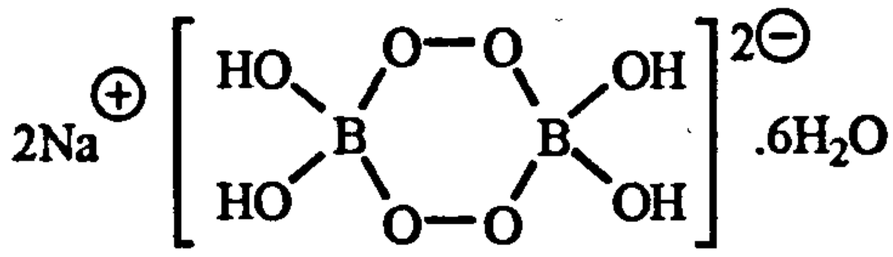
Some problems in stain removal are caused by the interaction between the textile and the chromophore; this is the case for both tea and wine stains that involve polyphenol-cotton interactions. Stain removal can also be a problem when the chromophoric material is located within a matrix; a good example of this is a curry stain where curcumin is trapped within a matrix of triglycerides, proteins, starches and remnants of meat and vegetables from the cooking process. Similarly, grass consists of chlorophyll located within chloroplasts of the cell. The presence of such a matrix can have a major effect in determining the ease of removal of a stain even if the matrix components themselves are removed relatively easily in the wash.

The problem faced by the formulator is how to deliver improved stain-removal from products to the consumer. This is because increased activity often means poorer storage stability. Compounds that are too aggressive can cause local dye damage, so bleaching activity must be balanced against dye fading properties.

1.4 Oxygen-based bleaches

A typical non-biological washing powder (Persil®) contains: soap, zeolites, polycarboxylates (less than 5 %), anionic and neutral surfactants (5-15 %), phosphates (15-30 %) and an oxygen-based bleaching agent (i.e. an *O*-transfer agent). A typical hard surface cleaner (Domestos® Multisurface Cleaner) consists of soap, surfactants, alkali, thickening agents and sodium hypochlorite as an aqueous solution at pH 12.5.

Oxygen-based bleaches can be divided into two general categories: hypochlorite bleaches (usually NaOCl) and peroxide bleaches, which are often present in cleaning formulations as perborate **(8)** or percarbonate **(9)**.



(8)

$2Na_2CO_3.3H_2O_2$

(9)

1.4.1 Sodium hypochlorite [sodium oxochlorate (I)]

Sodium hypochlorite has been used as a bleach since the late eighteenth century and it is the most effective, commercially available bleach known. Commercial sodium hypochlorite solutions are prepared by the passage of chlorine gas through aqueous sodium hydroxide **[1]**.

$$2\,NaOH + Cl_2 \longrightarrow NaOCl + NaCl + H_2O \quad [1]$$

The bleaching activity of 'sodium hypochlorite' is actually due to the electrophile, hypochlorous acid (HOCl), which predominates even at the high pH of household bleach. Sodium hypochlorite is a very powerful oxidising agent, making it extremely efficient at both soil removal and stain decolourisation. Sodium hypochlorite is effective in low concentrations against a wide range of soil types, it is a broad-spectrum biocide (frequently present at a low level in domestic water supplies) and it is very cheap. Sodium hypochlorite bleach is effective in several key areas: it decolourises pigments (mildew, wine and tea stains etc.), it aids detergency by breaking-up the soil matrix (e.g. baked on cooker-hob soil) and kills micro-organisms (this is a key criterion for WC cleaning and for food preparation surfaces).

Being a very aggressive oxidant, sodium hypochlorite is not very selective, so if used in laundry applications it can cause damage to certain textile fibres and dyes, especially protein-based natural fibres like wool or silk. Nevertheless hypochlorite is very effective for hard-surface cleaning where it not only decolourises pigments but also aids detergency (oxidised stain species are more water-soluble) and kills micro-organisms.

Recently environmental concerns have led to calls for a reduction in the use of chlorine and chlorinated compounds. Sodium hypochlorite is acutely toxic to aquatic life and vegetation; furthermore it can react with organic matter in water and sewage

to form toxic by-products such as trihalomethanes, halogenated acetic acids, chlorinated ketones, chlorinated furanones and other chlorine-containing organics. Although these substances are normally present only in the range of parts per billion (ppb), they have caused considerable concern because several of them are known or suspected carcinogens.[4,5] Furthermore, chlorine-containing organics are known to persist in the environment and over time they accumulate in the fats of animals. More than 170 chlorinated organics have been detected in the mothers' milk, semen, blood and breath of the general U.S. and Canadian populations. They are known to mimic or otherwise disrupt hormones and can interfere with the endocrine system. Even tiny doses could thus potentially affect reproduction, development, and behaviour.

There are other general safety concerns: sodium hypochlorite is extremely reactive and if it is mixed with other cleaning products a mixture of toxic gases can be liberated. When household chlorine bleach (a sodium hypochlorite solution) is combined with an acid or acid-producing substance, such as a toilet bowl cleaner or vinegar, there is a sudden release of a quantity of chlorine gas. Likewise, when chlorine bleach is mixed with ammonia, lye, or other alkaline substance, a highly irritating gas is produced.

Hypochlorite is used in several areas around the home. Domestos® is an example of a commercially available bleach used for stain removal; it typically contains a 4-5 % solution of sodium hypochlorite. General-purpose kitchen cleaners contain a 1-2 % sodium hypochlorite solution and typically encounter a wide variety of food deposits, hydrophilic stains and hydrophobic, fatty stains. Mould and mildew removers contain a 2-3 % sodium hypochlorite solution for the removal of pigmented fungal spores and hyphae; there is considerable variation in the ease of bleaching between different mould species.

Another unpleasant characteristic of sodium hypochlorite is that it has a strong odour. It is difficult to mask this with perfume in household products, in part because hypochlorite will oxidise the perfume!

1.4.2 Hydrogen peroxide

Hydrogen peroxide was discovered more than 180 years ago by Thénard[6] and it is now produced on a megaton scale.[7] Hydrogen peroxide is one of the commonest

bleaches; it is the fourth cheapest oxidant and is the least expensive source of active oxygen. Hydrogen peroxide is a much more environmentally friendly oxidant than sodium hypochlorite because water is the only by-product formed from it. Sodium perborate, sodium percarbonate and urea-hydrogen peroxide are solid sources of hydrogen peroxide that have no shock sensitivity and exceptional storage stability. The annual production of both sodium perborate and sodium percarbonate now approaches six-figure tonnages.[8] Both are non-toxic and neither the reagents nor their reduction products pose an environmental hazard.

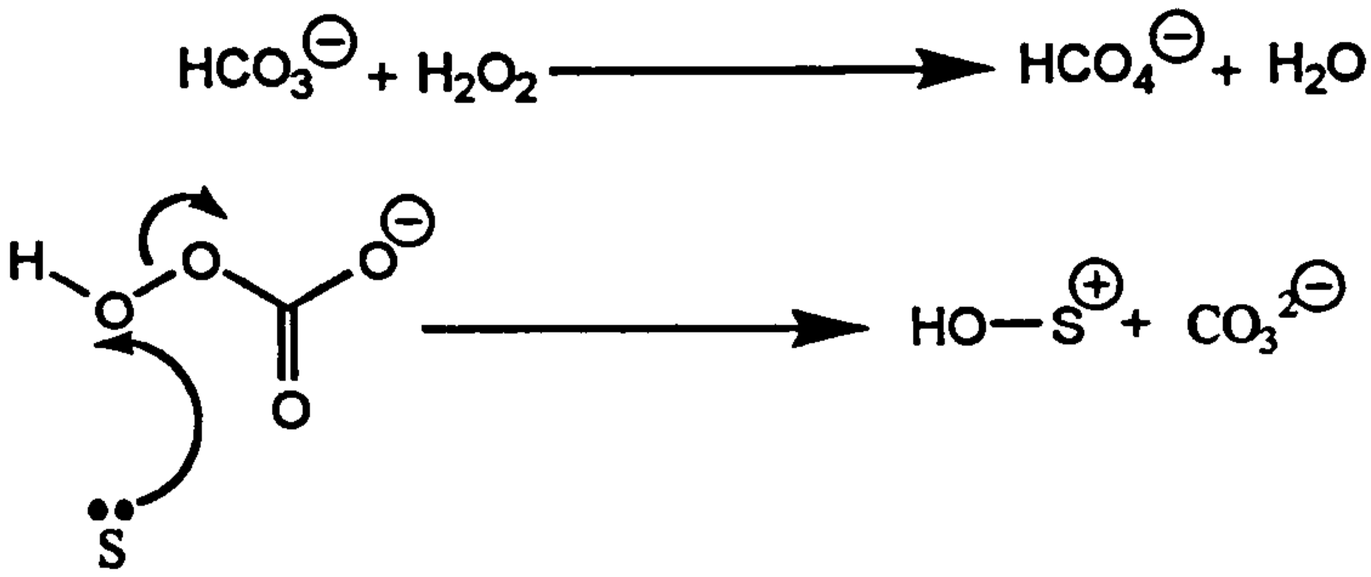
Hydrogen peroxide is often present in washing powders as sodium perborate tetrahydrate ($NaBO_3.4H_2O$) and its first use was in Germany in 1909 for Henkel's Persil® product. Sodium perborate tetrahydrate is synthesised by the treatment of a borax solution with hydrogen peroxide and sodium hydroxide **[2]**. Dissolution of perborate in water causes its hydrolysis and the resulting formation of hydrogen peroxide (typically pH 9.5-10). One advantage of using sodium perborate tetrahydrate is that it has a much longer 'shelf-life' than sodium hypochlorite or aqueous hydrogen peroxide since the borate component helps to stabilise the material against decomposition.

$$Na_2B_4O_7 + 2\,NaOH + 4H_2O_2 + 11H_2O \longrightarrow 4NaBO_3.4H_2O \quad [2]$$

Another highly stable source of hydrogen peroxide is sodium percarbonate,[9] which is synthesised from sodium carbonate and hydrogen peroxide in the presence of a stabiliser (such as sodium metasilicate).[10, 11] Sodium percarbonate is a peroxyhydrate and can act as a source of anhydrous hydrogen peroxide; it has been found that the liberation of H_2O_2 from sodium percarbonate can be achieved at a convenient rate even if the bulk of the compound does not dissolve in the organic solvent.[12] For example, if SPC is stirred with DCM or chloroform at room temperature, an equilibrium concentration of ca. 5 $mmol.L^{-1}$ of H_2O_2 is achieved. In THF a concentration of 16 $mmol.L^{-1}$ is achieved within 10 minutes. The addition of small amounts of water to the solvents increases the concentration of H_2O_2; saturation with water increases the concentrations to 22 and 29 $mmol.L^{-1}$ in DCM and chloroform respectively.

The true percarbonate anion has been detected only in minor amounts in aqueous solutions of sodium percarbonate.[13] The percarbonate anion would be

expected to behave as an electrophile (**Scheme 1.1**) and any deviation in oxidation activity would probably be caused by its presence. However solutions of sodium percarbonate behave like those of alkaline hydrogen peroxide since the perhydroxyl anion is formed at this pH.

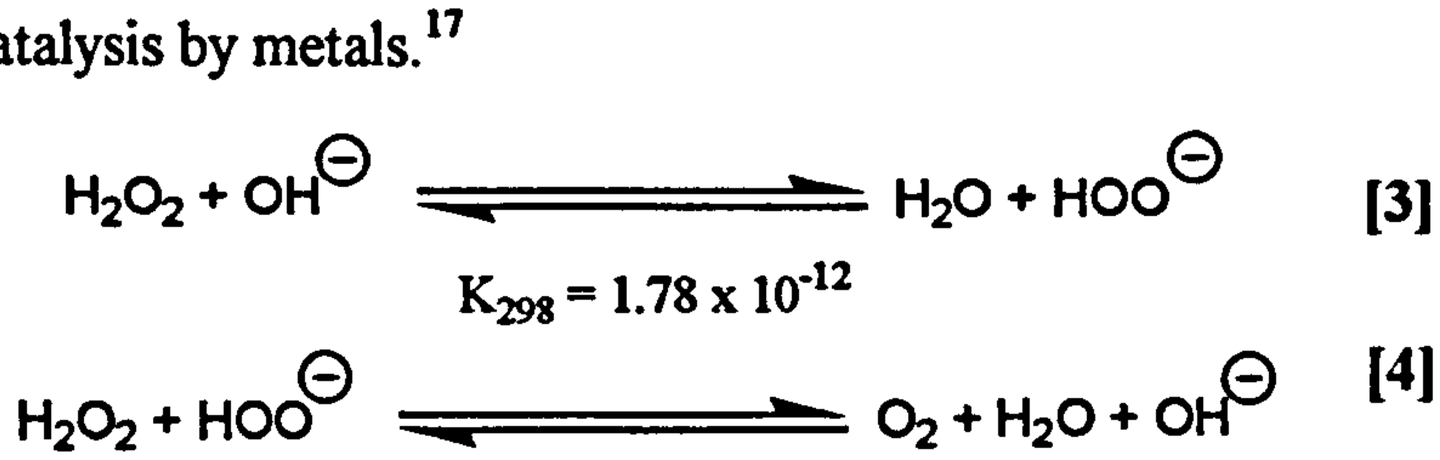


Scheme 1.1 Electrophilic oxidation by percarbonate anion

The urea-hydrogen peroxide complex (UHP) has also been widely used as a safe source of anhydrous hydrogen peroxide for the oxidation of many organic substrates.[14] This compound was first prepared by Tanatar[15] and was shown to be an adduct with formula **(10)**. Commercially it has been used for the whitening of teeth and skin blemish treatments.

(10)

Hydrogen peroxide is a less effective bleach than sodium hypochlorite and requires either high temperatures (95°C) or a high pH in order to achieve acceptable performance. Hydrogen peroxide is a very weak acid[16] and in alkaline medium it is partially converted to its hydroperoxide anion **[3]**. The alkaline pH necessary to increase the nucleophilicity of hydrogen peroxide means a short 'shelf-life' because hydrogen peroxide is not stable in aqueous alkaline solution **[4]**. Furthermore, although hydrogen peroxide is stable with respect to its elements, it is unstable with respect to water and molecular oxygen (**Figure 1.1**) and this decomposition is very sensitive to catalysis by metals.[17]



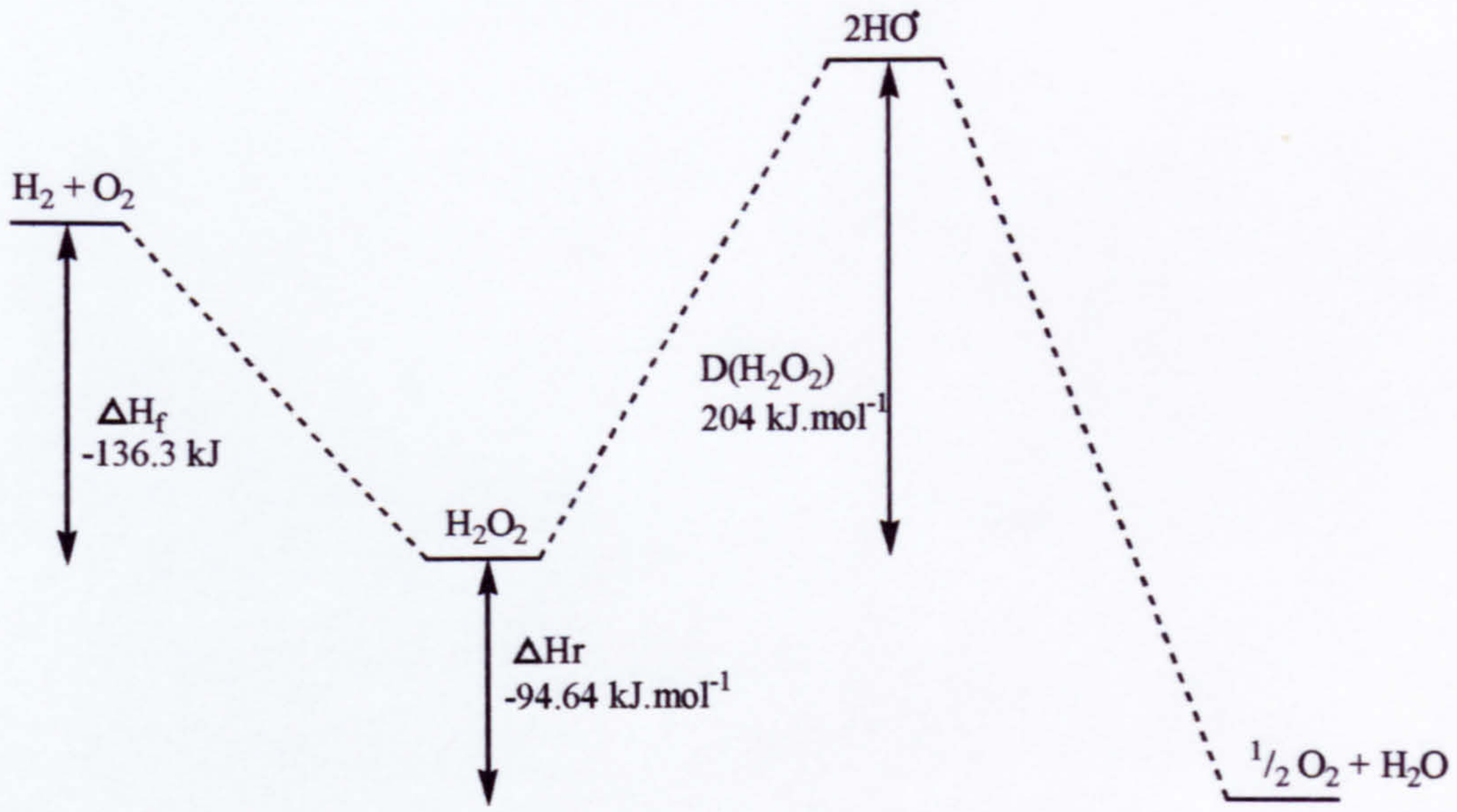


Figure 1.1 Energy profile of H_2O_2

When used in laundry applications, hydrogen peroxide bleach is safe for most coloured fabrics, but it is ineffective for stain removal at temperatures below 60°C (**Figure 1.2**). However, the bleaching power of hydrogen peroxide at low temperatures can be improved by the use of activators. For example, tetraacetylethylenediamine[18] [TAED; **(11)**] reacts with hydrogen peroxide to form peracetic acid '*in situ*' (**Scheme 1.2**) and thus lowers the wash temperature to between 40 and 60°C. TAED is the most commercially successful activator and it is present in more than 60 % of European detergents.

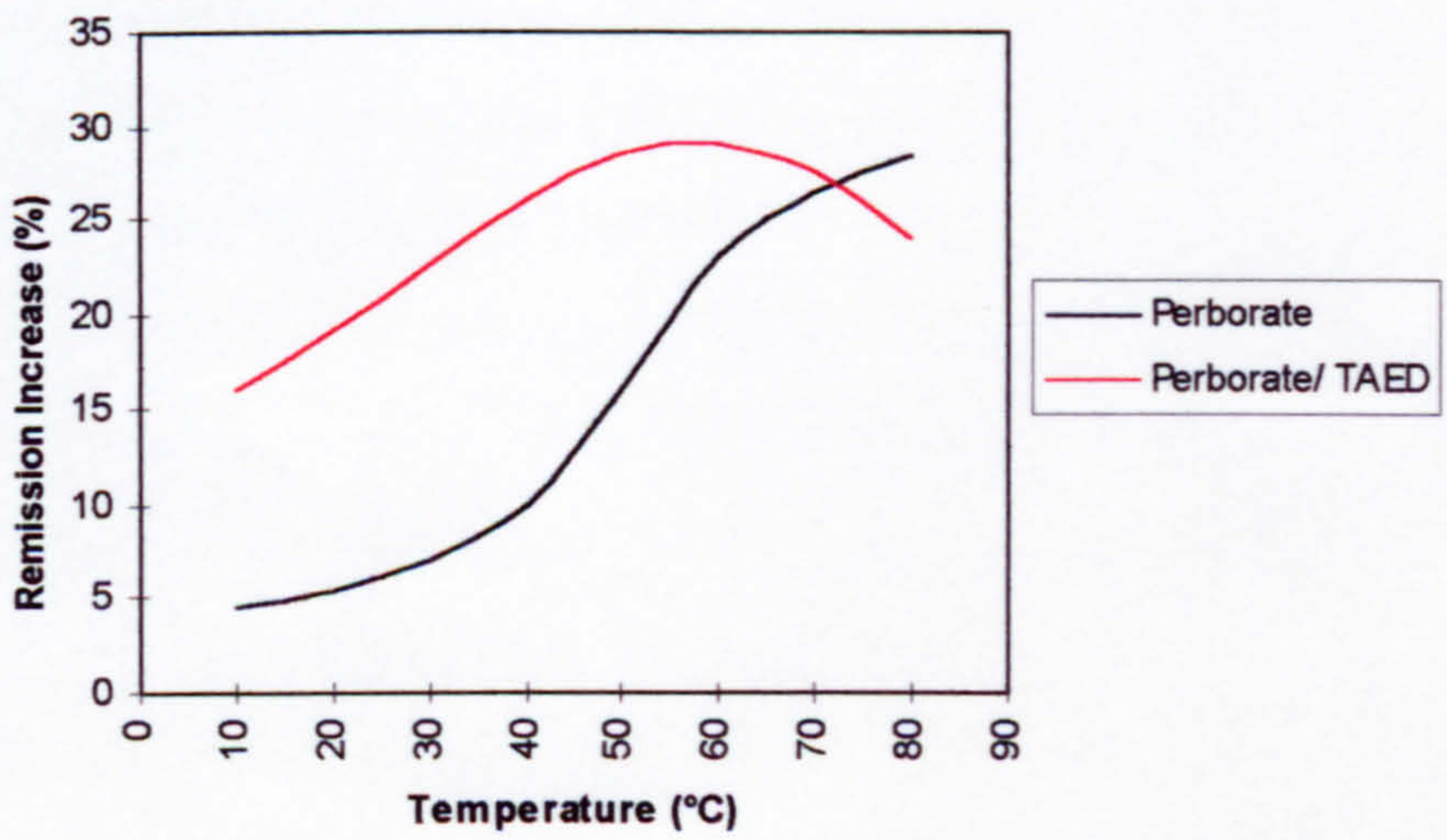
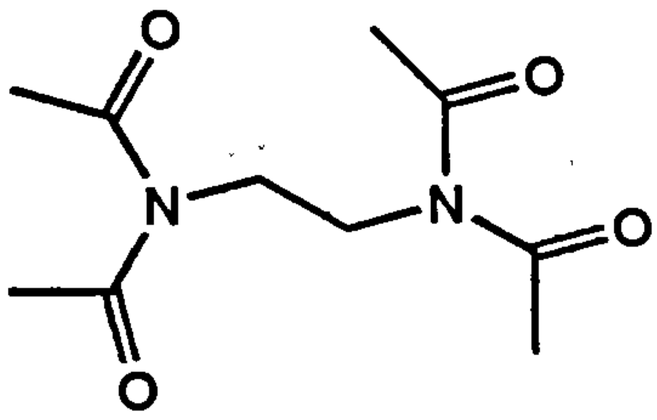
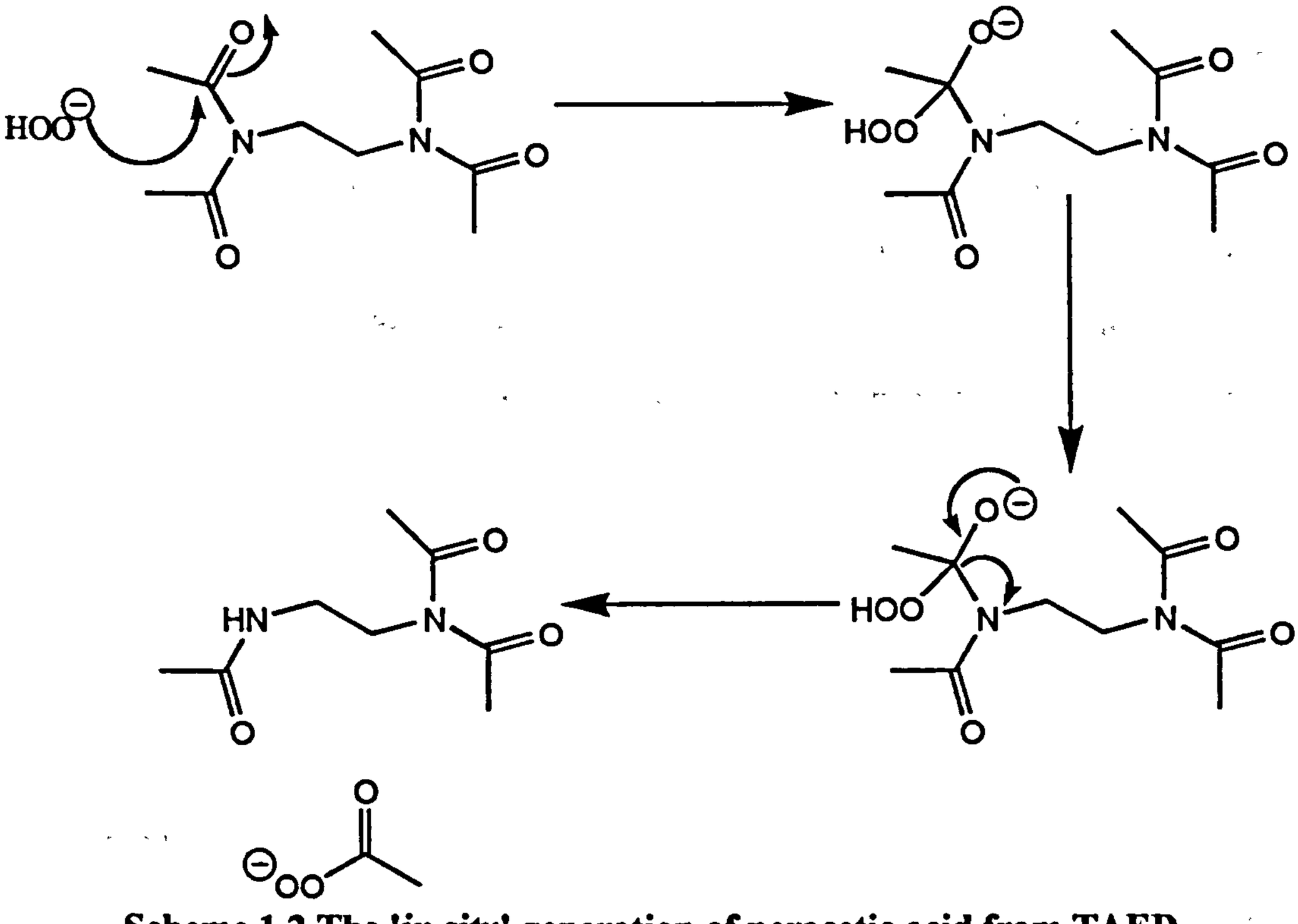


Figure 1.2

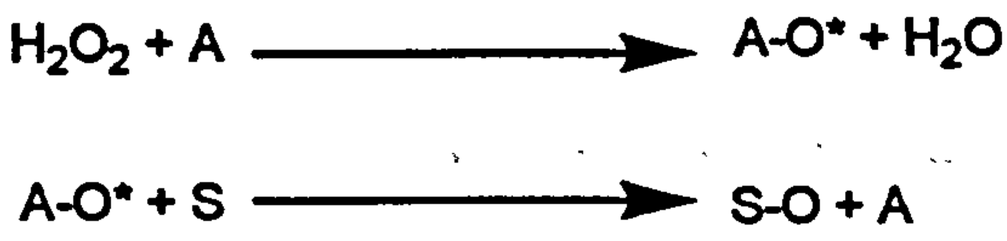


(11)



Scheme 1.2 The '*in situ*' generation of peracetic acid from TAED

For hard-surface cleaning and low temperature laundry applications the bleaching power of hydrogen peroxide needs to be improved; it should be possible to achieve this by the use of activators. The activator must be able to react with hydrogen peroxide to form an oxygen transfer agent **[5]**, which is more reactive towards substrates than hydrogen peroxide itself. In the case of laundry bleaching, selectivity is more important since damage to fibres can occur; however a sufficiently wide range of activity is required in hard-surface cleaning applications because a wide range of soil types will be encountered.



[5]

Where A = activator
S = substrate

The use of TAED is not appropriate for hard-surface cleaning because although peroxycarboxylic acids show enhanced lipophilicity over hydrogen peroxide and enhanced reactivity over hydrogen peroxide in fabric bleaching studies, they show poor activity against common household soils (e.g. mould, kitchen soils, model WC soils).

Since hydrogen peroxide is hydrophilic, other organic molecules (activators) such as peroxy acids must be used to transfer oxygen to hydrophobes such a grass stain. In wash water the surface of a stained textile has a negative charge which increases as the pH of the wash-water increases. This helps the separation of stains from the fabric, but the negative charge will also repel hydroperoxide and percarboxylate anions. Besides an increase in wash-temperature, another way to ensure that the bleach comes into contact with the stained fabric is to use an electrophilic bleach which is attracted to the fibre. Peroxy acids containing quaternery ammonium groups have been developed by Unilever and used for this purpose;[19] other organic, electrophilic oxidants should also be effective in this area.

1.4.3 Oxone® (12)

This compound is a source of potassium monopersulfate ($KHSO_5$) that is marketed as a chlorine free bleach by Dupont.[20] It has a high oxidation potential which allows many oxidations to take place at room temperature; the standard electrode potential (E°) of Oxone® is shown in **[6]**.

$$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$$

(12)

$$HSO_4^{\ominus} + H_2O \rightleftharpoons HSO_5^{\ominus} + 2H^{\oplus} + 2e^{\ominus} \quad -1.44\ V \quad [6]$$

Oxone® is a relatively stable source of active oxygen which loses less than 1 % of its activity per month if stored under appropriate (cool, dry) conditions. However, Oxone® undergoes very slow decomposition, liberating oxygen gas and a small amount of heat. The stability is reduced by the presence of moisture, alkaline chemicals, chemicals which contain water of hydration and transition metals in any form. The decomposition of Oxone® is exothermic and this can cause the decomposition to accelerate if conditions allow the temperature to rise. If the

decomposition of Oxone® is associated with high temperatures, the constituent salts of Oxone® may generate sulfuric acid, sulfur dioxide, or sulfur trioxide.

Oxone® is acidic and so it is usually blended with alkaline salts to buffer it to near-neutral or slightly alkaline pH for use in cleaning products. Oxone® has been used for a wide variety of products and processes, especially those in which the convenience of a solid product is required. It is used commercially for many purposes: denture cleansing, paper recycling, cleaning of pools and spas, printed circuit board etching, laundry bleaching, and environmental applications i.e. for the replacement of hypochlorite.

1.4.4 Molecular oxygen/ air

Air is the cheapest oxidising agent; however it consists of only 21 % O_2 (by volume) or 23 % (by weight) and the preparation of pure oxygen from air is difficult. The most common methods for the preparation of oxygen are the fractional distillation of liquid air or the electrolysis of water.

Neutral water saturated with oxygen is quite a good oxidising agent [7], it can oxidise Cr^{2+} to Cr^{3+}, although this does not occur in pure water. In the presence of air, Fe^{2+} is slowly oxidised to Fe^{3+} in acidic solution, and this occurs even more rapidly in basic solution.

$$O_2 + 4H^{\oplus} + 4e^{\ominus} \rightleftharpoons 2H_2O \quad +0.815\ V \qquad [7]$$

For many reactions of O_2 there is a high activation energy, which is caused by several factors. Firstly, single electron transfer is thermodynamically unfavourable at both high [8] and low [9] pH with weak reducing agents.

$$O_2 + e^{\ominus} \rightleftharpoons O_2^{\ominus} \quad -0.33\ V \qquad [8]$$

$$O_2 + H^{\oplus} + e^{\ominus} \rightleftharpoons HO_2 \quad -0.13\ V \qquad [9]$$

Furthermore, the triplet ground state of O_2, with both π^* orbitals singly occupied, is neither an effective Lewis acid, nor an effective base. Therefore it does not undergo displacement reactions with *p*-block electrophiles or nucleophiles. Also, the high bond

energy of O_2 (463 kJ mol^{-1}) gives a high activation energy for reactions involving its dissociation.

Even though the potential of many reactions of oxygen is favourable, their rate is often slow. Heterogeneous catalysis or biocatalysis can increase the rate of oxidation and this has often been achieved by transition metals. In the presence of certain transition metal ions, O_2 can be co-ordinated in a metal complex and become more reactive than free oxygen gas. A problem in using O_2 as an oxidant is the fact that commonly only one oxygen atom is incorporated into the products of oxidation and the other reacts with a reducing agent (e.g. an aldehyde) so forming by-products in stoichiometric amounts.

The use of oxygen as an oxidising agent is too expensive and impractical. The use of air is made difficult by the limited solubility of oxygen in water (1 L of water will dissolve 48.9 mL O_2 at 1 atm; 2 $mmol.L^{-1}$) and the use of catalysts is associated with by-product formation and toxic metal containing waste.

There are other electronic states of oxygen that are more reactive than the triplet ground state. Of the two singlet states of O_2, only one has a long enough lifetime to participate in chemical reactions. $O_2(^1\Delta_g)$ can be generated either chemically or photochemically. It is usually generated chemically by the disproportionation of hydrogen peroxide **[10]**. Photochemical production involves the use of a coloured sensitiser to absorb energy from the light source and transfer it to triplet oxygen, thus generating $O_2(^1\Delta_g)$. This method is unacceptable for both laundry and hard-surface bleaching because of the strongly coloured sensitiser that is necessary.

$$H_2O_2 + Cl_2 \longrightarrow 2\overset{\ominus}{Cl} + 2\overset{\oplus}{H} + O_2 \qquad \textbf{[10]}$$

1.4.5 Ozone

Ozone is a much more powerful oxidising agent than O_2; in acid solution there are few stronger oxidants **[11]**. Ozone can be made in concentrations up to 10 % from O_2 by the action of electrical discharge; pure ozone can be obtained by fractional liquefaction of such mixtures. Traces of O_3 are formed in the upper atmosphere by the action of UV light on O_2. At ground level, ozone is regarded as a pollutant, and it has

been associated with outbreaks of asthma in cities, where it is created when by-products of fossil fuels react with sunlight.

[11]

Although the high reactivity of ozone would be useful for hard-surface cleaning, it may damage fabrics if used in laundry bleaching. In addition the use of ozone for hard surface or laundry cleaning is not possible because of the practical difficulties in generating ozone.

1.5 Electrophilic oxidants

Electrophilic oxidants are useful for the oxidation of negatively charged or nucleophilic substrates. Examples of electrophilic oxidations in organic synthesis are sulfoxidation, epoxidation and *N*-oxidation. The oxidation of sulfides to sulfoxides was chosen as the model reaction in the present investigation, since this oxidation is electrophilic and selectivity can be monitored easily because over-oxidation (to sulfone) is easily detected.

Sulfides are responsible for many of Nature's most repugnant smells - the removal of these smells could be achieved by oxidation of the offending species. Organosulfur compounds occur naturally in many foodstuffs and they are also the products of biological decay. Sulfur containing compounds are found in garlic, onions, radishes, asparagus, chives, cabbage, leeks, cress, turnip, mustard, truffles, coffee, tea and pineapples among many others. There has been speculation that many animals have developed olfactory sensitivity to organosulfur compounds through natural selection as a form of protection against the ingestion of decaying food.

There has been some recent work showing how the detoxification of chemical warfare agents, such as mustard gas, can be achieved by the oxidation of the sulfide moiety within such molecules.[21]

Furthermore, there has been expanding interest in sulfoxides because they are useful as synthons, auxiliaries[22] and ligands[23] in organic synthesis. Although there are many different methods for the preparation of sulfoxides,[24] there are only a small number of genuinely convenient, generally applicable procedures. The most attractive, most general approach to sulfoxides is the selective catalytic oxidation of the corresponding sulfides.

The growing importance of chiral sulfoxides stems from the fact that homochiral sulfoxides are able to control the formation of new stereogenic centres[25] before being removed under mild conditions (e.g. by reduction, β-elimination, Pummerer-type reactions, alcoholysis).[26] Asymmetric oxidation of prochiral sulfides is the simplest and most attractive method for the synthesis of homochiral sulfoxides, but the synthesis of optically-active sulfoxides has often proved difficult. For brevity, the following chapter will discuss only those oxidations of sulfides to sulfoxides that are relevant to household cleaning applications and the removal of stains.

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Chapter 2

The Environmentally-Friendly

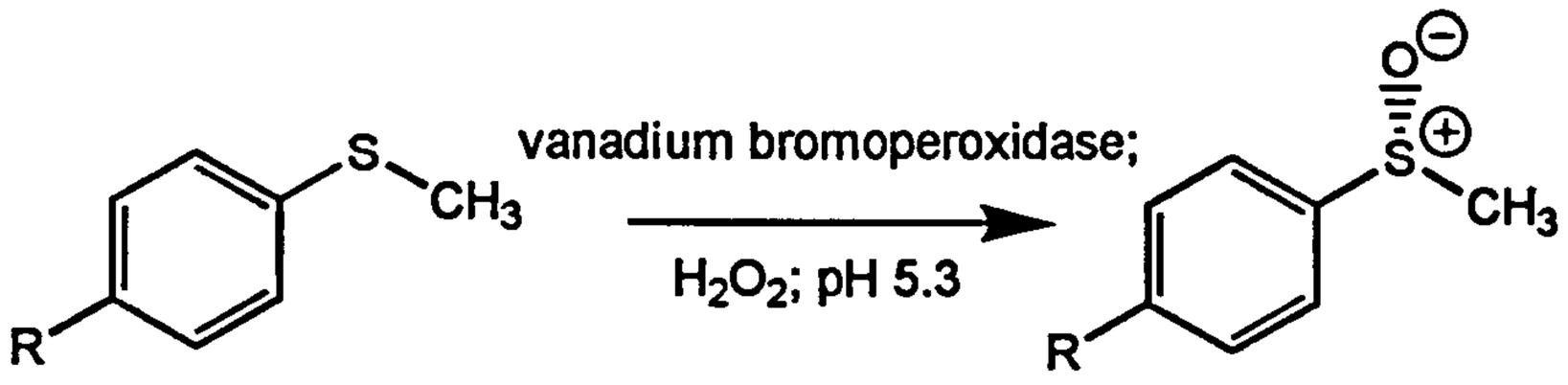
Oxidation Of Sulfides To Sulfoxides

2.1 Introduction

The focus in this chapter will be on the oxidation of sulfides (taken as a model stain) to sulfoxides, concentrating on the activation of the environmentally friendly oxidant hydrogen peroxide, by the '*in situ*' generation of selective oxidising species having increased activity and selectivity in the catalytic oxidation of sulfides. Sulfides are relevant as model stains because, for example *S*-amino acid residues are found in protein containing soils (e.g. eggs and milk in the kitchen, the outer coatings of some types of mould and mildew and faeces in the W.C.).

The oxidation of sulfides to sulfoxides was achieved using hydrogen peroxide in 1908.[1] Other oxidants[2] that have been used for this process include organic hydroperoxides, peracids, peroxides, nitrogen oxide derivatives (e.g. nitric acid, nitrates), 'positive' halogen derivatives (such as NBS), enzymes and other oxidising species (e.g. Oxone®).

The most important methods for the oxidation of sulfides to sulfoxides are reviewed below. Many examples of the preparation of homochiral sulfoxides are given because most recent reports are aimed at this area for the reasons mentioned earlier. Only one example of an enzymatic method has been included (**Scheme 2.1, Table 2.1**) because, although excellent selectivity has been achieved in some cases, the substrate generality of enzymes is often poor.



Scheme 2.1

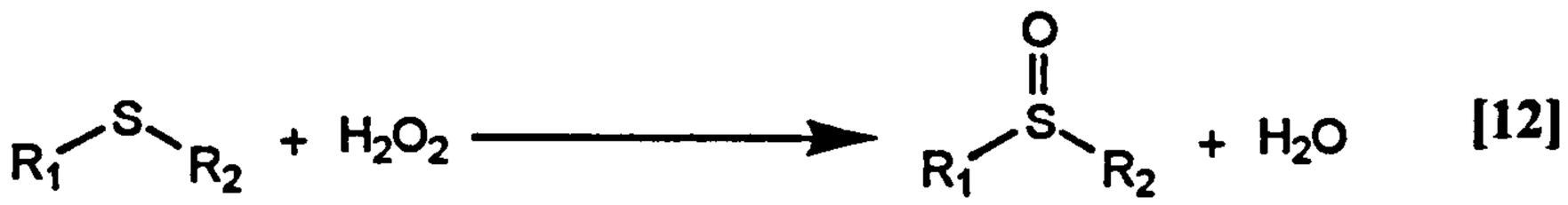
Table 2.1 Sulfoxidation of *p*-substituted methyl phenyl sulfides by vanadium bromoperoxidase from *A. nodosum* at pH 5.3[3]

R	Conversion[a] (%)	ee (%)	Configuration
NH_2	51	89	R
CH_3	18	82	R
H	71	76	R
Br	21	47	R
Cl	97	54	R

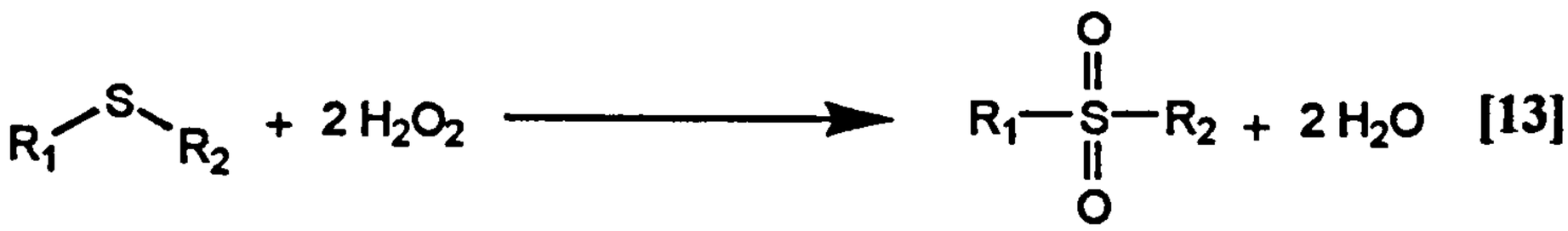
[a] based on production of sulfoxide

2.2 Hydrogen peroxide

The most widely used reagent for the oxidation of sulfides is hydrogen peroxide, used either alone or with an activator. The products of oxidation are either the sulfoxide **[12]** or the sulfone **[13]** depending upon the reaction conditions used.



[12]

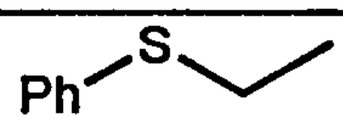
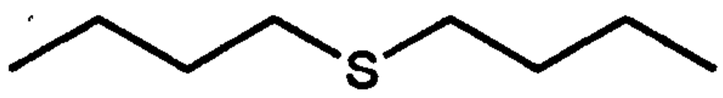
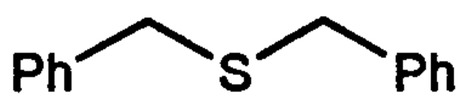
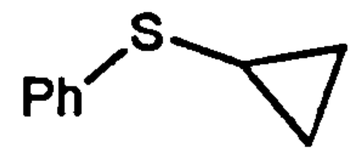
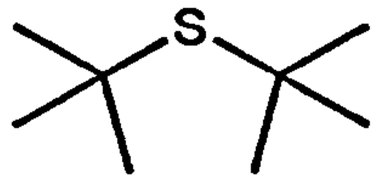
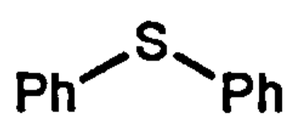
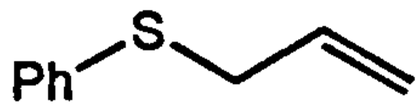
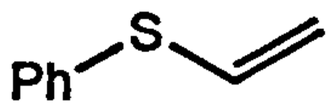
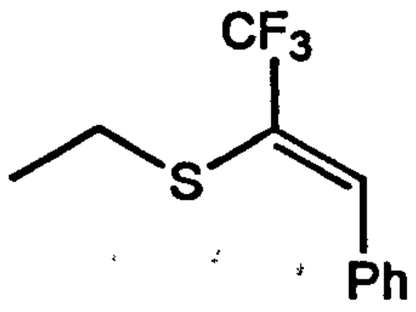
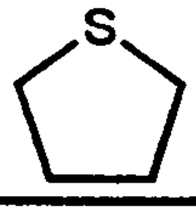


[13]

The oxidation of sulfides to sulfoxides by hydrogen peroxide was originally carried out in acetone solution, but the use of methanol was subsequently shown to increase the rate of reaction.[4] This method has been used to prepare a large number of sulfoxides selectively and the mild conditions employed mean that even acid-sensitive sulfoxides, such as allyl sulfoxides, have been successfully prepared. Recently,[5] the urea-hydrogen peroxide complex has been used for the oxidation of sulfides (as well as hydroxylated aldehydes and ketones, nitriles and nitrogen heterocycles) under solvent free conditions.

Hexafluoropropan-2-ol has been used as a solvent to facilitate the selective oxidation of sulfides to sulfoxides by aqueous hydrogen peroxide.[6] The authors suggest that its mode of action is to form strong hydrogen bonds with hydrogen peroxide (activating the hydroxyl leaving group) and with the oxygen of the sulfoxide (preventing any further oxidation).

Table 2.2 The oxidation of sulfides with aqueous hydrogen peroxide in hexafluoropropan-2-ol[6]

Substrate	Time (mins)	Yield (%)
	5	97
	5	92
	5	98
	5	93
	20	97
	5	99
	5	99
	15	94
	5	98
	5	82

2.3 Activation of hydrogen peroxide

The catalysis of hydrogen peroxide mediated oxidations has been reported many times, in particular by acids (as acylating agents or proton sources) and metal salts.

2.3.1 Acids

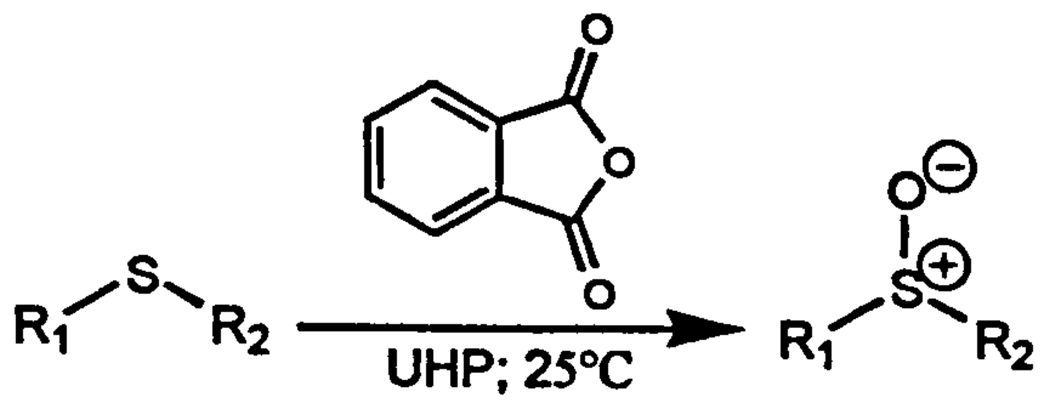
Many acids, both inorganic and organic, have been shown to catalyse the oxidation of sulfides to sulfoxides. For example, acetic, sulfuric and perchloric acids all catalyse the oxidation of sulfides and other substrates by hydrogen peroxide. The active oxidant is either $H_3O_2^+$ or a peracid formed '*in situ*'. Organic peracids, such as *meta*-chloroperbenzoic acid, have been used directly to oxidise sulfides for many years[7] and are still used today.[8] However, such compounds are not very stable[9] and have high safety and cost considerations. For some metal salts, the active oxidant is also thought to be a peracid.

The oxidation of some alkyl aryl sulfides by hydrogen peroxide catalysed by sulfuric, perchloric and methanesulfonic acids has been studied recently.[10] It was found that the rate constants for oxidations of sulfides increases more rapidly than

the stoichiometric concentration of the acid, as for many acid-catalysed reactions. In the case of sulfuric acid, the observed catalysis could be caused by: equilibrium protonation of hydrogen peroxide, a kinetic solvent effect of sulfuric acid, or the formation of peroxymonosulfuric acid. Perchloric acid does not form a peroxyacid in aqueous solution with hydrogen peroxide, but it does catalyse the oxidation of sulfides, presumably by the formation of $H_3O_2^+$. Methanesulfonic acid is considerably less effective than sulfuric or perchloric acids in catalysing this oxidation, as would be expected from its lower protonating power. The authors found that plots of the rate constants against Hammett's acidity function ($-H_0$) are linear and conclude that protonation of hydrogen peroxide is the most important factor in oxidations of this type. Peroxymonosulfuric acid is only formed when the concentration of sulfuric acid is greater than 50 wt.%.

2.3.2 The '*in situ*' generation of peracids

There are many organic compounds, containing acyl groups (e.g. TAED (**11**), see earlier), that have been used in conjunction with hydrogen peroxide to generate peracids '*in situ*' and thus effect the conversion of sulfides to sulfoxides. For example, phthalic anhydride has been used to activate hydrogen peroxide in the oxidation of sulfides to sulfoxides[11] **(Scheme 2.2; Table 2.3)**. More recently[12] trifluoroacetic anhydride has been used with UHP to oxidise sulfides to sulfones.

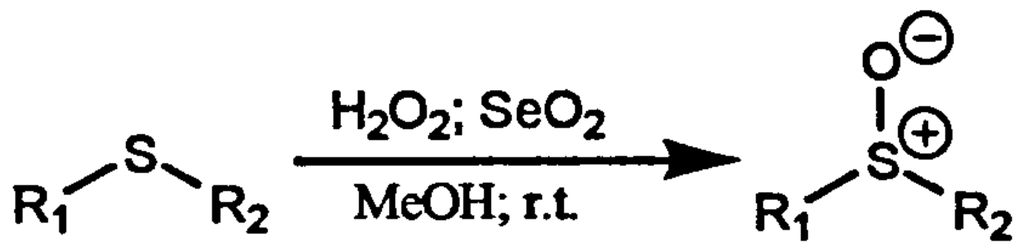


Scheme 2.2

Table 2.3 The oxidation of sulfides by phthalic anhydride/ UHP

R_1	R_2	Time (hours)	Yield (%)
n-C_3H_7	*n*-C_3H_7	2	84
n-C_4H_9	*n*-C_4H_9	2	94
t-C_4H_9	*t*-C_4H_9	3	92
CH_3	C_6H_5	3	90
t-C_4H_9	CH_3	2	89
Ph-CH_2	Ph-CH_2	2	92
Ph-CH_2	C_6H_5	3	94
C_6H_5	C_6H_5	3	95
2-NO_2-C_6H_4	C_6H_5	4	92

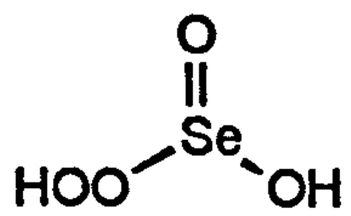
Certain metal salts are also thought to form peracids '*in situ*' by reaction with hydrogen peroxide. For example, selenium dioxide is believed to catalyse the oxidation of sulfides *via* perselenic acid **(13)** generation[13]. In the example given, the sulfoxides are formed after one minute.



Scheme 2.3

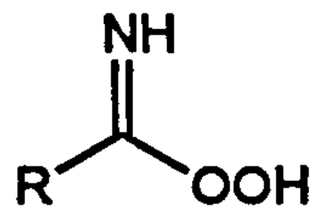
Table 2.4 The oxidation of sulfides by selenium dioxide/ hydrogen peroxide

R_1	R_2	Yield (%)
CH_3	*i*-C_4H_9	82
n-C_4H_9	*n*-C_4H_9	90
$C_6H_5CH_2$	$C_6H_5CH_2$	94
CH_3	C_6H_5	95
i-C_3H_7	C_6H_5	97
i-C_4H_9	C_6H_5	95
CH_3	4-CH_3-C_6H_5	94
C_6H_5	C_6H_5	92



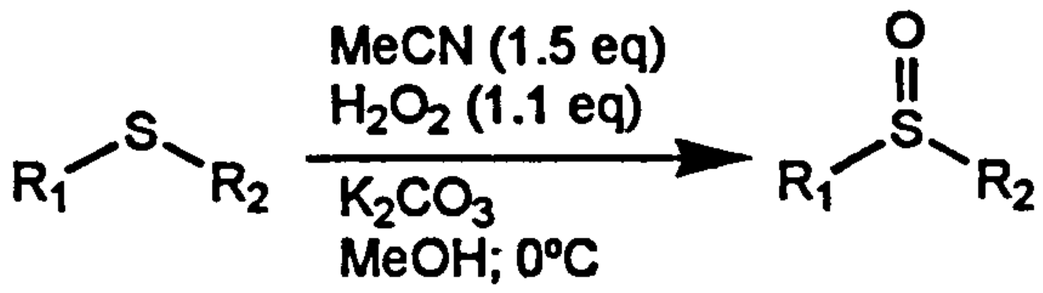
(13)

Bethell and Page have studied the Gagnieu modification of the non-catalytic Payne oxidation system with potassium carbonate and its application to the oxidation of sulfides.[14] In this process the active intermediate is thought to be a peroxyimidic acid **(14)** generated from the reaction of hydrogen peroxide with acetonitrile **(Scheme 2.4)**.



(14)

The chiral nitrile, (+)-2-heptaheliceonitrile, has been used in a Payne-type oxidation of (*E*)-stilbene and α-methylstyrene, giving excellent results (greater than 97 % ee).[15] However, the preparation of this nitrile was very lengthy, and, since the catalyst was not recoverable at the end of the reaction, chiral product is obtained at the expense of the chiral nitrile. Furthermore, the oxidant used was 98 % hydrogen peroxide, ruling this out as a general approach.

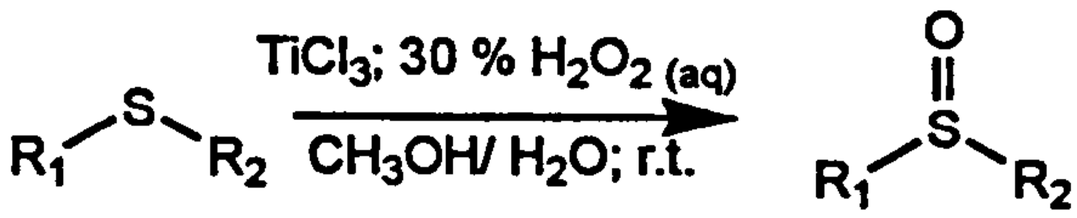


Scheme 2.4

2.3.3 Transition metals

Transition metal complexes have been used as catalysts for the oxidation of sulfides to sulfoxides, often with very high enantioselectivity. However they have often been carried out using oxidants other than hydrogen peroxide,[16] which are not environmentally friendly, and so will not be considered here. For example, the most widely used method for catalytic asymmetric sulfoxidation, a modification of the Sharpless[17] technique for the epoxidation of allylic alcohols developed independently by Kagan[18] and Modena,[19] utilises *t*-butyl hydroperoxide as the oxygen source.

Most procedures for the oxidation of sulfides catalysed by titanium species are based on Kagan's method and so rely on *t*-butyl hydroperoxide as the primary oxidant.[20] However, sulfides have also been selectively oxidised to sulfoxides by titanium trichloride and hydrogen peroxide (**Scheme 2.5**).[21] This simple procedure gives excellent yields in less than five minutes and the pure sulfoxides are isolated with ease (**Table 2.5**).



Scheme 2.5

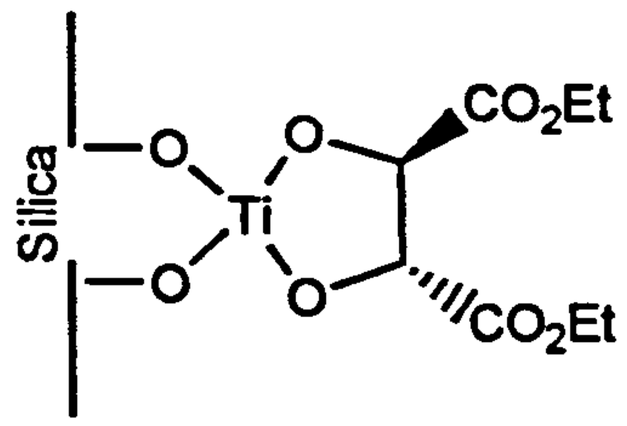
Table 2.5 Oxidation of sulfides by titanium (III) chloride and hydrogen peroxide

R_1	R_2	Reaction time	Molar ratio (sulfide/ H_2O_2/ $TiCl_3$)	Yield (%)
t-C_4H_9	*t*-C_4H_9	5 min	1/ 10.5/ 2	95
CH_3	C_6H_5	5 min	1/ 7/ 2	100
C_6H_5	$C_6H_5CH_2$	5 min	1/ 7/ 2	98
CH_3	4-NO_2-C_6H_5	10 min	1/ 7/ 2	100
4-CH_3-C_6H_5	4-CH_3-C_6H_5	15 min	1/ 7/ 2	98
C_6H_5	C_6H_5	5 min	1/ 5.6/ 2	100
C_6H_5	CH_2CN	15 min	1/ 7/ 2	95
2-pyridyl	CH_3	5 min	1/ 7/ 2	93

Titanium derivatives supported on silica have been used to oxidise sulfides to sulfoxides with high yields and good selectivity,[22, 23] however only small asymmetric inductions are observed in the presence of chiral ligands such as tartrate (**Table 2.6**).[24] The reaction was carried out at 25 °C in methanol with 187 mg catalyst per mmol of sulfide and 30 % aqueous hydrogen peroxide as the oxygen source. The authors suggest that the catalyst's structure is that shown in **(15)**.

Table 2.6 The oxidation of sulfides by supported titanium catalysts

R_1	R_2	Reaction time (hours)	Yield (%)	Sulfoxide/ sulfone ratio
4-CH_3-C_6H_5	CH_3	24	97	97: 3
n-C_4H_9	*n*-C_4H_9	4	100	-
CH_3	*t*-C_4H_9	24	97	97: 3
-$(CH_2)_4$-		4	98	98: 2
C_6H_5	$C_6H_5C(O)$	24	94	99: 1
C_6H_5	C_6H_5	24	97	98: 2
C_6H_5	$CH=CH_2$	24	97	97: 3



(15)

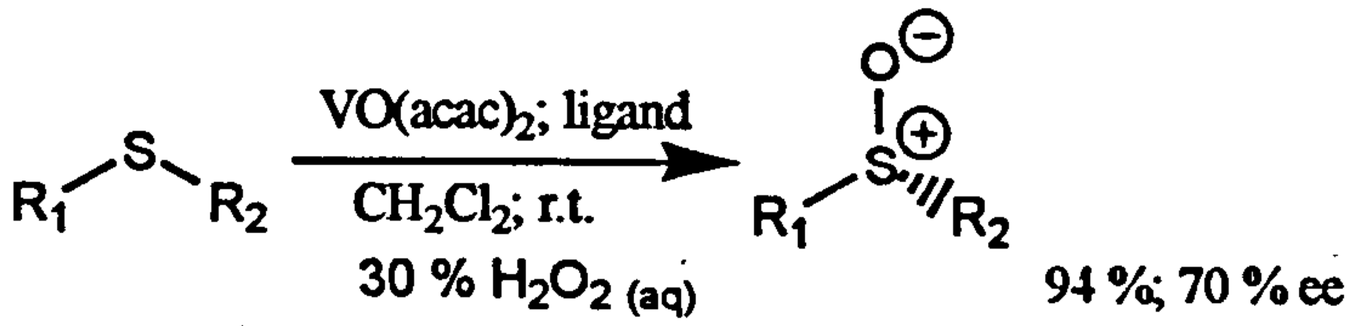
Titanium containing zeolites have been used to activate hydrogen peroxide towards the oxidation of sulfides to both sulfoxides and sulfones.[25] The authors found that for the oxidation of sulfides with TS-1 and Ti-β by hydrogen peroxide, the use of DBU was necessary to prevent the rapid non-catalysed reaction. This system was also used for the selective sulfoxidation of allyl methyl sulfide with no

epoxidation occuring. However, this method is restricted to substrates which are small enough to enter the micropores of the catalyst.

Table 2.7 Oxidation of butyl methyl sulfides with TS-1 in the presence of DBU at 21°C for 24h

Substrate	Conversion (%)	Selectivity		Ratio sulfoxide: sulfone
		Sulfoxide	Sulfone	
n-Bu-S-CH_3	52.1	79.3	20.7	3.8
i-Bu-S-CH_3	49.5	88.9	11.1	8.0
s-Bu-S-CH_3	47.8	90.4	9.6	9.4
t-Bu-S-CH_3	51.7	93.8	6.2	15.1

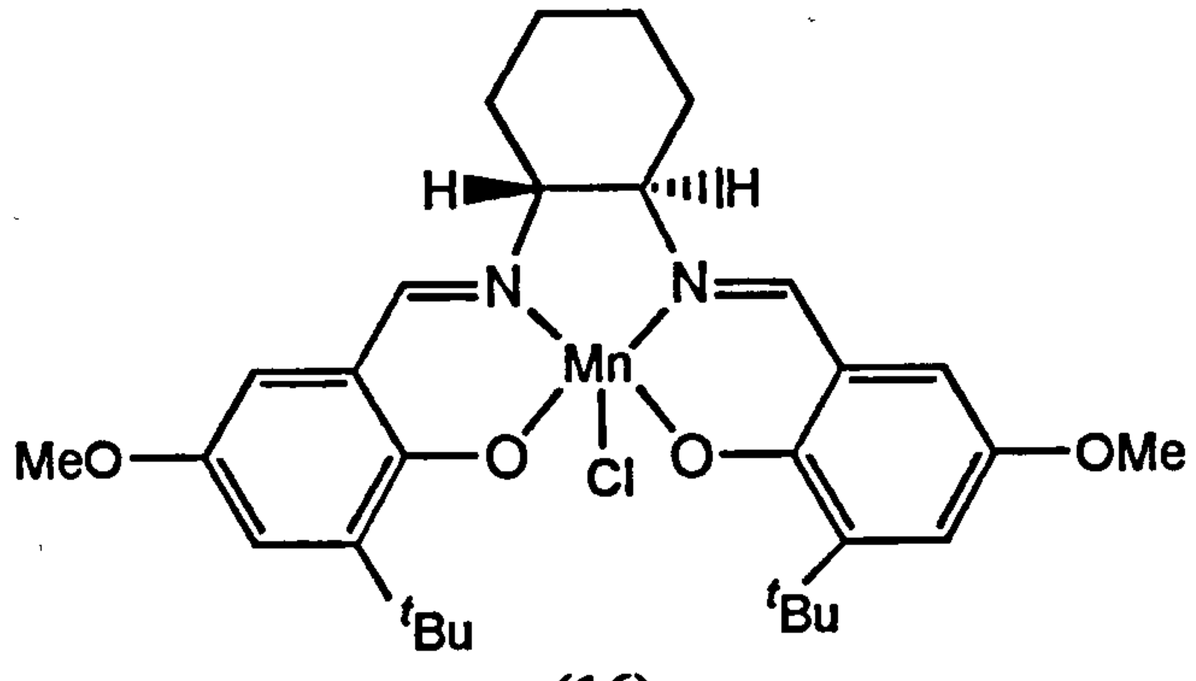
Several vanadium salts have been used to oxidise sulfides to sulfoxides in good yield using hydrogen peroxide as the oxidant.[26, 27] More recently, Bolm[28] has used vanadyl diacetylacetonate (less than 1 mole %) in conjunction with a chiral salicylaldehyde-derived ligand to produce optically active aryl alkyl sulfoxides (ee's up to 70 %) in this way (**Scheme 2.6**). The enantiomeric excesses were later improved by the use of alternative ligands.[29]



Scheme 2.6

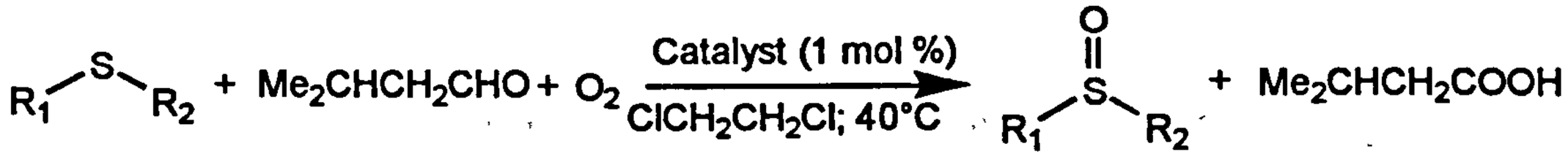
There are no examples in the literature of the oxidation of sulfides by hydrogen peroxide catalysed by chromium complexes.

(Salen) manganese (III) complexes **(16)** have been used to produce optically active sulfoxides in good yields with high levels of asymmetric induction. Jacobsen[30] discovered that optically active (salen) manganese (III) complexes are effective mediators for the catalysis of hydrogen peroxide oxidations of sulfides with moderate enantioselection (up to 47 %). However most approaches[16, 31] utilise hypervalent iodine reagents (such as iodosylbenzene), which are expensive and unstable, as the oxygen sources. Indeed, when Katsuki used hydrogen peroxide, under Jacobsen's conditions, as the oxidant the yields were much lower.[31] Experiments using *meso*-tetraphenylporphyrin complexes of manganese (III) also give incomplete oxidation of sulfides when using aqueous hydrogen peroxide.[32] Work by Mukaiyama has utilised molecular oxygen in conjunction with a (salen) manganese (III) complex to oxidise sulfides[33] in good yield with reasonable enantiomeric excesses (44- 72 %).



(16)

Sulfides have been oxidised to sulfoxides using molecular oxygen and aldehydes in the presence of a transition metal catalyst **(Scheme 2.7)**.[34] The molecular oxygen was present at 1 atm, the most effective sacrificial aldehyde proved to be isovaleraldehyde and the sulfone was only produced in relatively small amounts. The authors suggest that the role of aldehyde may be to form an organic peracid '*in situ*', which is converted to the acid in the oxidation process.



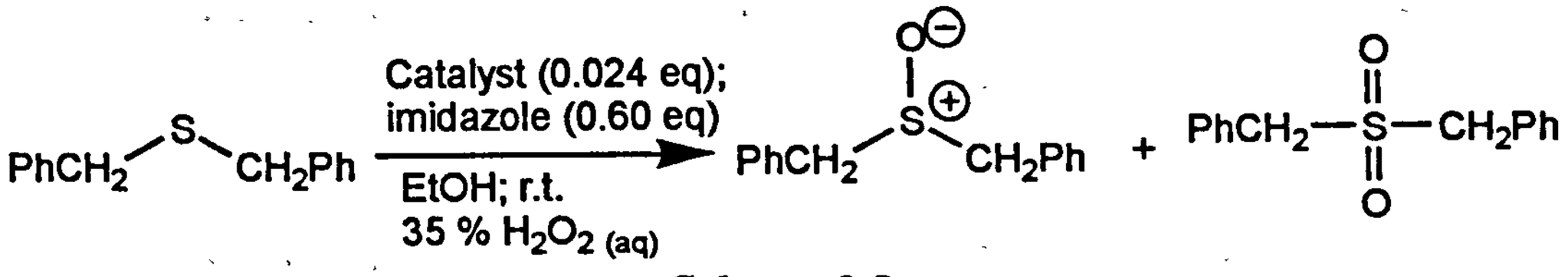
Scheme 2.7

Table 2.8 The oxidation of sulfides catalysed by transition metal salts in the presence of isovaleraldehyde

Catalyst	R_1	R_2	Reaction time (hours)	Yield of oxidation products (%)	
				Sulfoxide	Sulfone
MnO_2	Et	Et	2	72[a]	4[a]
MnO_2	Ph	Ph	4	66	trace
$Cu(OH)_2$	Et	Et	2	76[a]	2[a]
$Cu(OH)_2$	Ph	Ph	4	47	trace
$Cu(OAc)_2$	Et	Et	1	75[a]	4[a]
$Cu(OAc)_2$	Ph	Ph	4	76	trace
Fe_2O_3	Et	Et	2	75[a]	10[a]
Fe_2O_3	Ph	Me	1	81	8
Fe_2O_3	Ph	Ph	4	65	trace

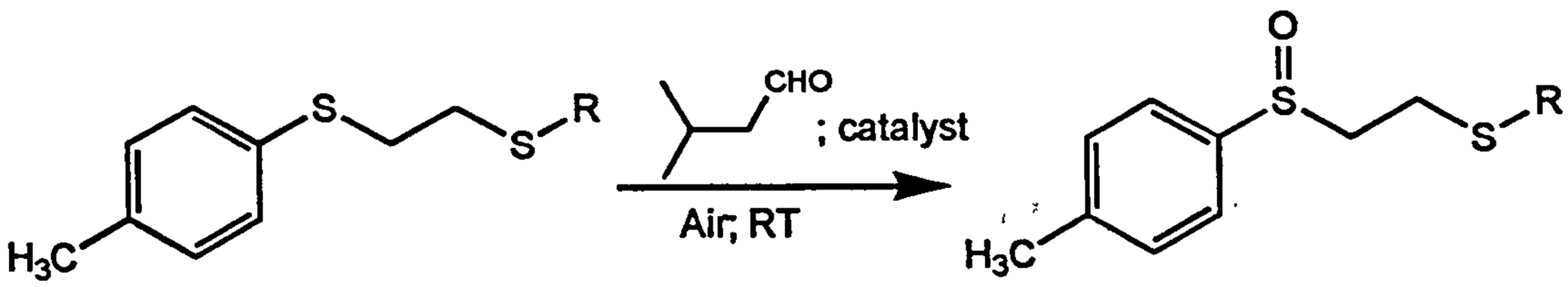
[a] GC yield

Iron (III) complexes of *meso*-tetraphenylporphirin (with imidazole as a co-catalyst) were shown to give complete conversion of phenyl alkyl sulfides to sulfones within five minutes after the addition of aqueous hydrogen peroxide **(Scheme 2.8)**.[32] However, iron (II) phthalocyanine is more selective and gives 93 % conversion to the corresonding sulfoxide in five minutes with no sulfone formation.



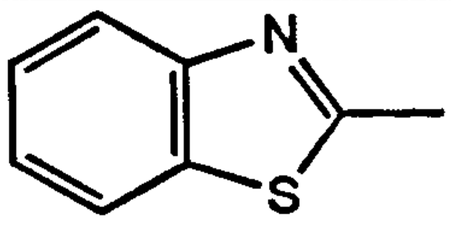
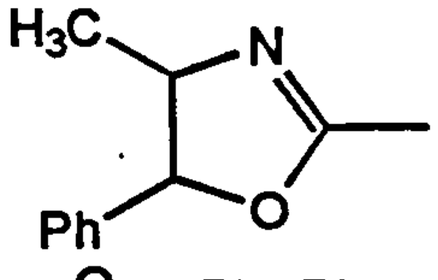
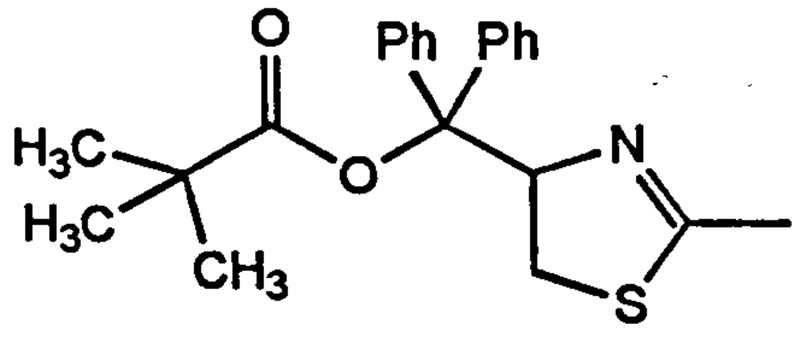
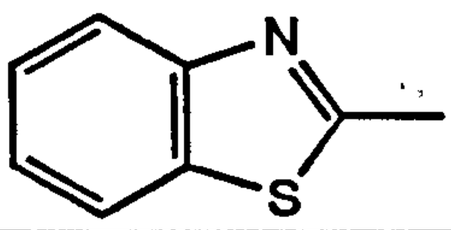
Scheme 2.8

Recently, cobalt (II) compounds have been used in conjunction with a sacrificial aldehyde and air to selectively oxidise some *bis*-sulfides to the corresponding sulfoxides (**Scheme 2.9**).[35] If the reaction time was prolonged, over-oxidation to the sulfone or *bis*-sulfoxide was observed, but the *bis*-sulfone was never observed.



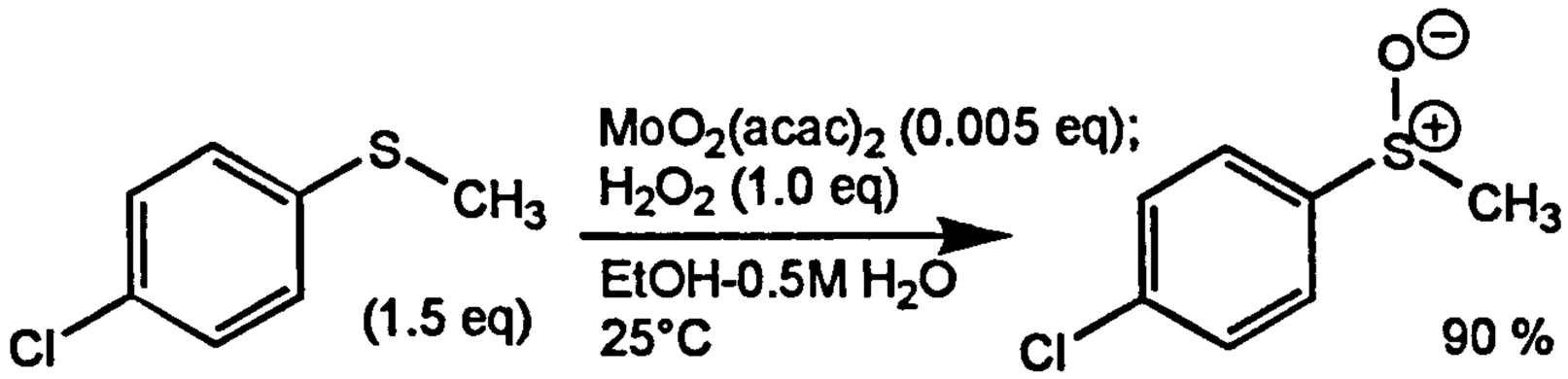
Scheme 2.9

Table 2.9 Oxidation of *bis*-sulfides by cobalt (II) compounds

R	Catalyst	Time (hours)	Yield of monosulfoxide (%)
	$Co(acac)_2$	8	95
	$Co(acac)_2$	7	90
	$Co(acac)_2$	23	90
	Co-(polymer)	20	93

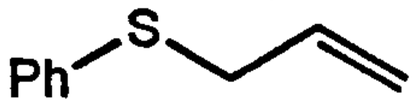
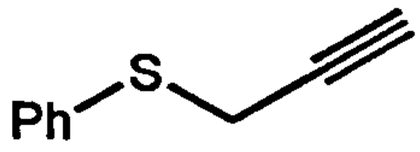
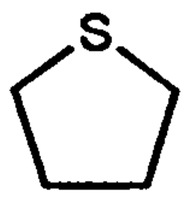
Chiral Schiff base complexes of nickel (II) and copper (II) have been used as catalysts for the oxidation of thioanisole employing aqueous hydrogen peroxide as the oxidant.[36] However only moderate conversions and very low ee's were achieved.

The molybdenum-catalysed oxidation of sulfides to sulfoxides by hydrogen peroxide has been studied by Modena *et al*,[37, 38] who discovered that the rate of reaction is independent of the Mo (VI) species initially added. The main complexes studied were $MoO_2(acac)_2$, $Mo(CO)_6$ and $MoO_5.HMPT.H_2O$ **(Scheme 2.10)**. More recently,[39] molybdenum salts have been immobilised on silica and used for the oxidation of aliphatic and aromatic sulfides with aqueous hydrogen peroxide as the oxidant **(Table 2.10)**.

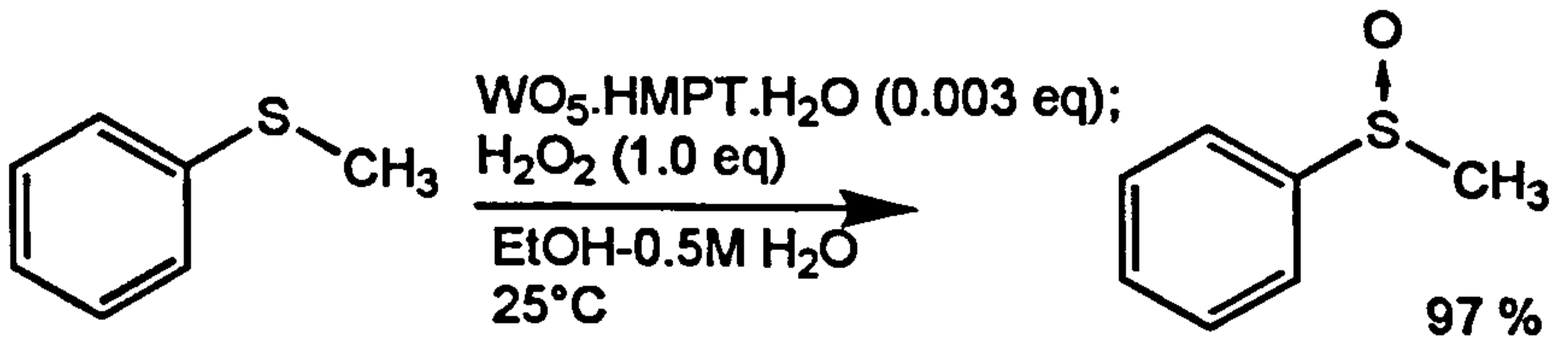


Scheme 2.10

Table 2.10 Oxidation of sulfides catalysed by MoS-1 [80]

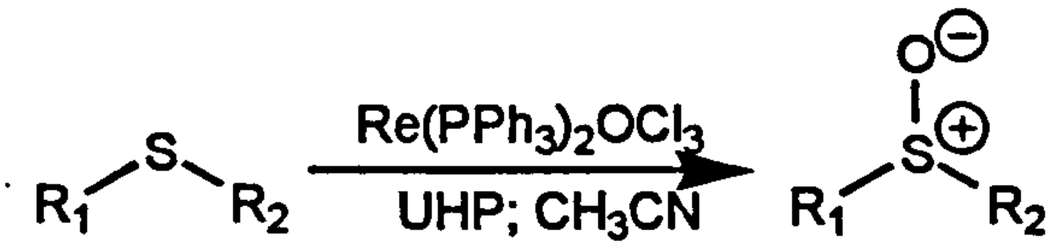
Substrate	Time (h)	Conversion (%)	Selectivity (%)
Me_2S	2	96	94
$(n\text{-}Bu)_2S$	3	98	93
PhSMe	3	93	90
Ph_2S	8	80	75
$(PhCH_2)_2S$	3	90	85
	7	89	85
	7	98	84
	2	98	94

The kinetics and mechanism of the oxidation of *p*-substituted phenyl methyl sulfides catalysed by tungsten (VI) compounds in conjunction with hydrogen peroxide has been investigated **(Scheme 2.11)**.[40] This study concludes that the hydrogen peroxide-tungsten (VI) system is an efficient oxidant and the rate-determining step is the transfer of oxygen from the metal complex to the sulfide. The same system was also found to oxidise cyclohexene and 1-methylcyclohexene.



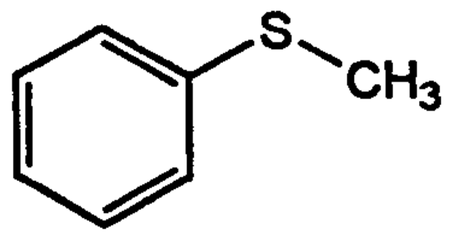
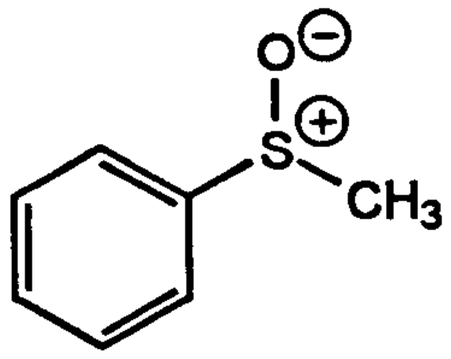
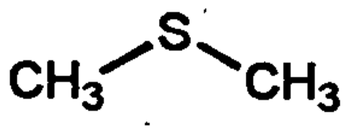
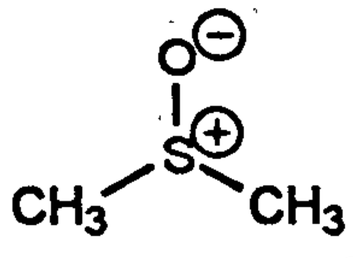
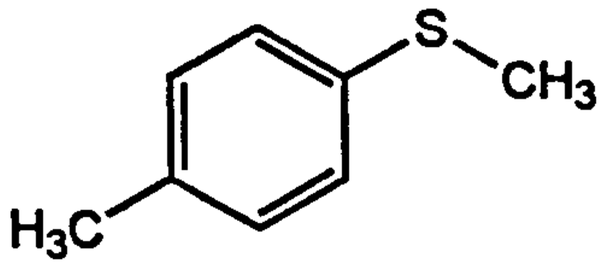
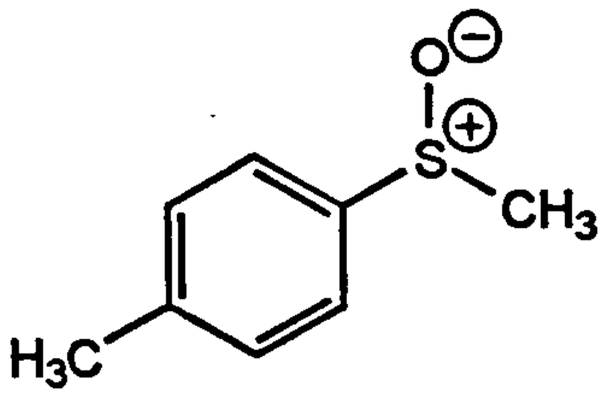
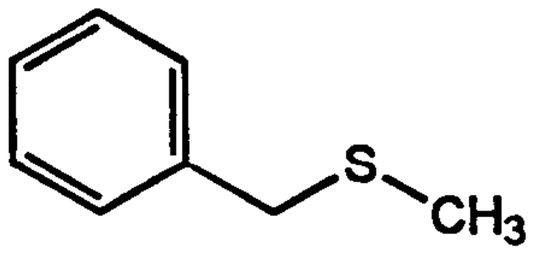
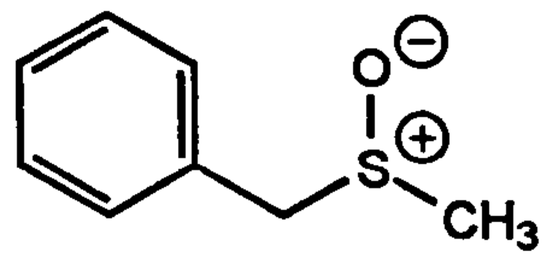
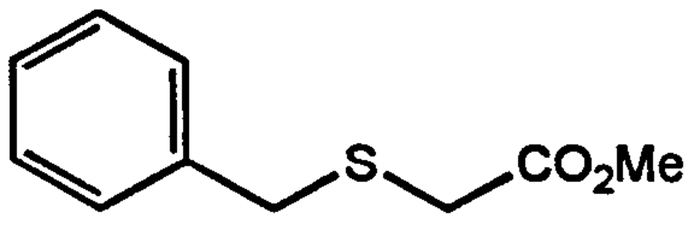
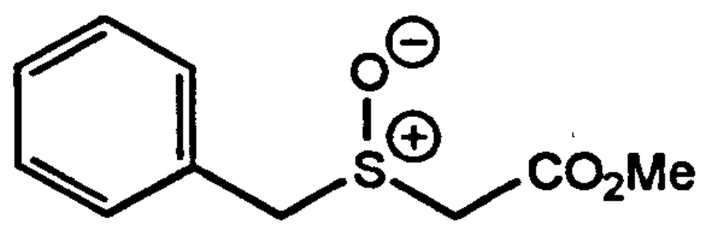
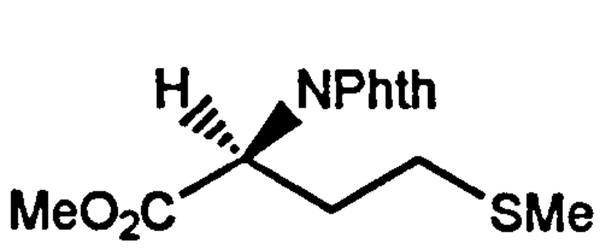
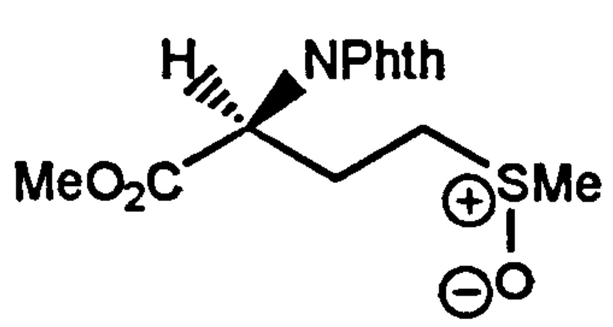
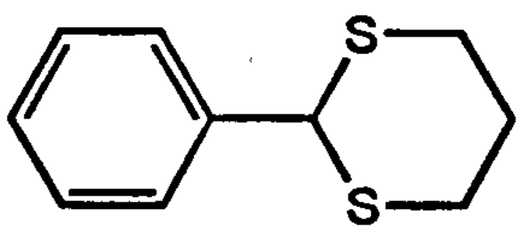
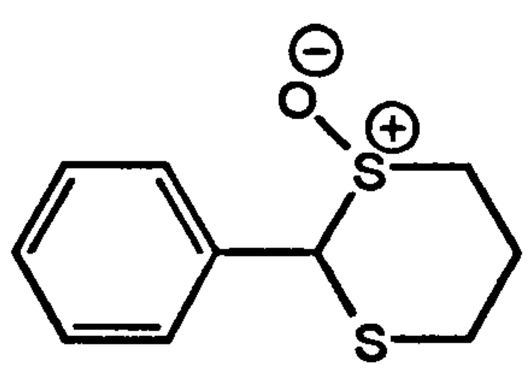
Scheme 2.11

Several rhenium (V) species have been employed as catalysts of hydrogen peroxide oxidations of sulfides to sulfoxides.[41, 42] Good yields of sulfoxides are obtained from oxidations using UHP catalysed by a rhenium (V) oxide phosphine complex in a simple procedure that requires little work-up **(Scheme 2.12)**.



Scheme 2.12

Table 2.11 Oxidation of sulfides with UHP catalysed by a rhenium (V) oxide phosphine complex

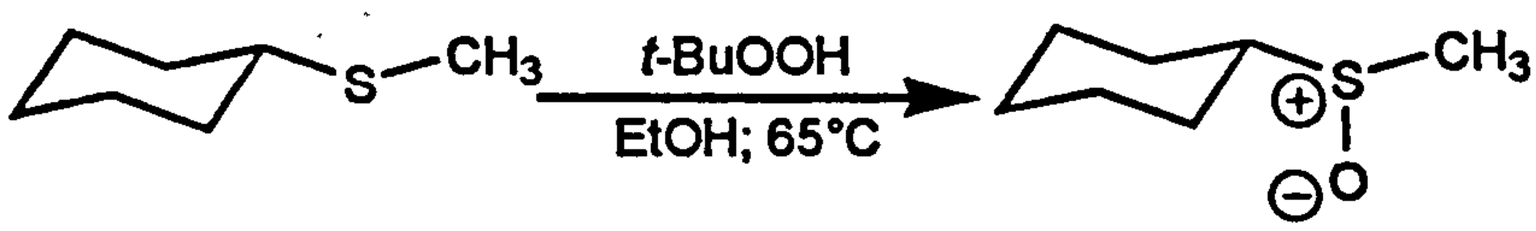
Substrate	Product	% Yield
		92
		90
		90
		90
		90
		80
		85[a], 88[b]

[a] yield of monosulfoxide
[b] yield of disulfoxide

Both ruthenium (II)[43] and ruthenium (III)[44] complexes have been shown to catalyse the oxidation of sulfides to sulfoxides by air. For example, $Ru^{III}L(H_2O)$ (L= EDTA, PDTA or HEDTRA) forms a complex with dimethyl sulfide which undergoes oxidation in air to form to a dimethyl sulfoxide complex with no over oxidation to dimethyl sulfone. However the authors note that aryl sulfides are much less reactive with $Ru^{III}L(H_2O)$ complexes.

2.3.4 The generation of organic hydroperoxides

Sulfides have been oxidised to sulfoxides using organic hydroperoxides since 1954.[45] This method is very successful for both olefins and sulfides, oxidising saturated sulfides in quantitative yield (**Scheme 2.13**). Alkyl hydroperoxides have also been used as sources of oxygen in catalysed sulfoxidations, particularly by transition metals (see earlier). However, the use of such compounds as primary oxidants is unacceptable environmentally since they are both toxic and hazardous. With regard to organic synthesis, the quantity of organic hydroperoxides used in a reaction must be carefully controlled in order to avoid over oxidation.



Scheme 2.13

An acceptable use of organic hydroperoxides would be to generate them '*in situ*' by reaction of an organic compound with hydrogen peroxide. 2-Hydroperoxyhexafluoro-2-propanol has been used for the direct oxidation of sulfides to sulfoxides or sulfones,[46] but it can be generated '*in situ*' from hydrogen peroxide and catalytic quantities of hexafluoroacetone.[47]

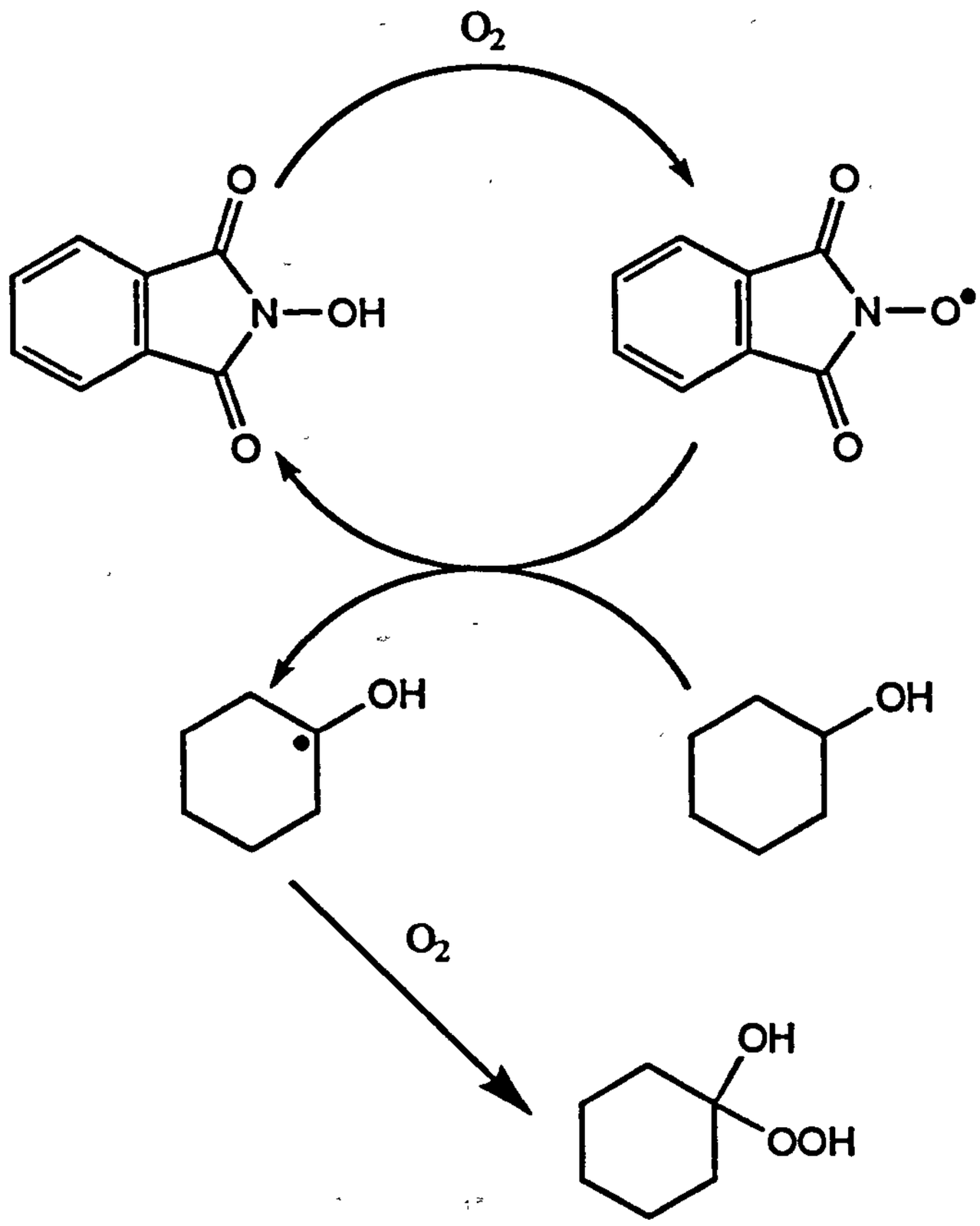
Catalytic 1,1,1-trifluoroacetone in conjunction with 35 % hydrogen peroxide has been used for the selective oxidation of sulfides to sulfoxides in nearly quantitative yields (**Table 2.12, Scheme 2.14**).[48] The authors suggest that the active oxidant is 2-hydroperoxy-1,1,1-trifluoro-2-propanol, although one could also envisage dioxirane formation.

Table 2.12 Sulfoxidation by hydrogen peroxide/ 1,1,1-trifluoroacetone

Sulfide	Time (min)	Yield of sulfoxide (%)
n-Bu_2S	15	98
	15	98
s-BuSPh	120	85
PhSMe	90	94
p-$HOCH_2C_6H_4SMe$	90	92
$(C_6H_5)_2S$	480	96
p-O_2N-$C_6H_4CH_2SC_6H_5$	300	95
p-CH_3O-$C_6H_4SCH_2C_6H_5$	120	93
$C_6H_5CH_2SC_6H_5$	150	90
$(C_6H_5CH_2)_2S$	90	98
p-$CH_3C_6H_4CH_2CH_2SC_6H_5$	120	96
$C_6H_5SCH_2COOH$	150	80

Scheme 2.14

The aerobic oxidation of sulfides to sulfoxides has been accomplished using *N*-hydroxyphthalimide in the presence of cyclohexanol.[49] An α-hydroxyhydroperoxide is formed '*in situ*' after hydrogen abstraction from cyclohexanol and subsequent reaction with dioxygen **(Scheme 2.15)**. The procedure requires a temperature of 90°C and a small amount of sulfone is formed.



Scheme 2.15

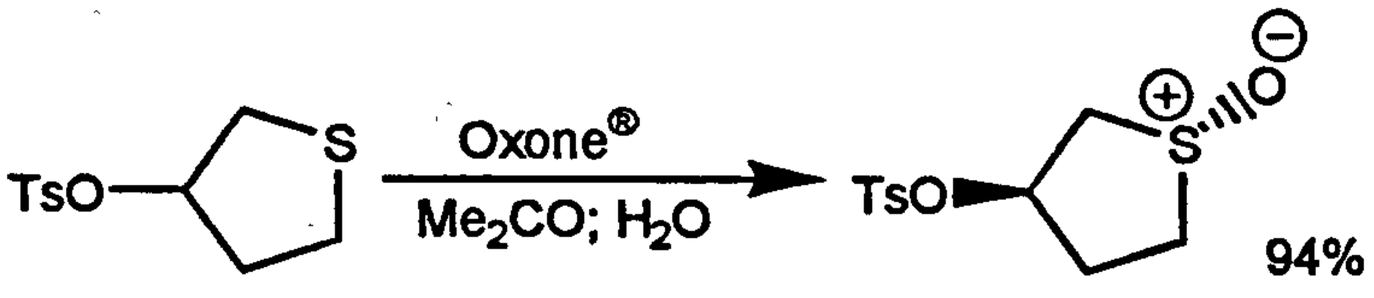
2.4 Other oxidants

Other oxidants that have been used to oxidise sulfides include nitrogen oxide derivatives, halogens and halogen derivatives. Indeed, nitric acid was used to oxidise a sulfide as early as 1865;[50] organic nitrates and inorganic nitrates, such as cerium ammonium nitrate (CAN) have been used more recently to give good conversions of sulfides. However, nitrates are well known as worldwide contaminants of ground and surface waters[51] so their use industrially is not acceptable.

Hypervalent halogen compounds (e.g. sodium metaperiodate, iodosobenzene) and electrophilic halogen sources (e.g. *N*-bromosuccinimide) have also been used to good effect in the oxidation of sulfides.[2, 52] The use of halogenated compounds is not acceptable environmentally for reasons mentioned earlier.

Dioxiranes have been used very successfully for the catalytic, enantioselective epoxidation of alkenes.[53] They are commonly generated '*in situ*' from Oxone® and a ketone, although they have been isolated. Methyl (trifluoromethyl) dioxirane has been used for the direct oxidation of sulfides, but sulfones are preferentially formed.[54]

Other chemical oxidants have been used for more chemo- and stereoselective sulfoxidation. Such oxidants include Oxone® (a source of potassium hydrogen persulfate[55]), oxaziridines and oxaziridinium salts. Oxone® gives a *cis / trans* ratio of 1: 15 for the oxidation of sulfide **(17)** in acetone **(Scheme 2.16)**.[56]



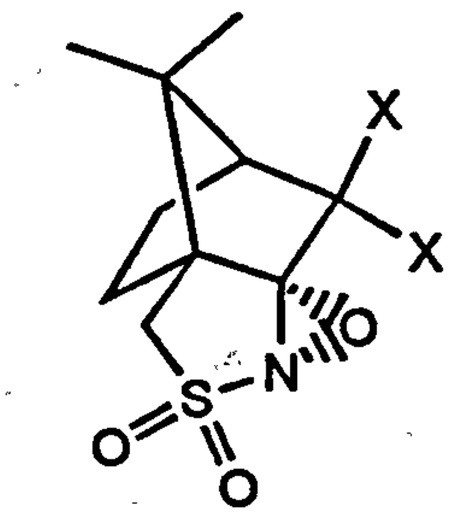
(17)

Scheme 2.16

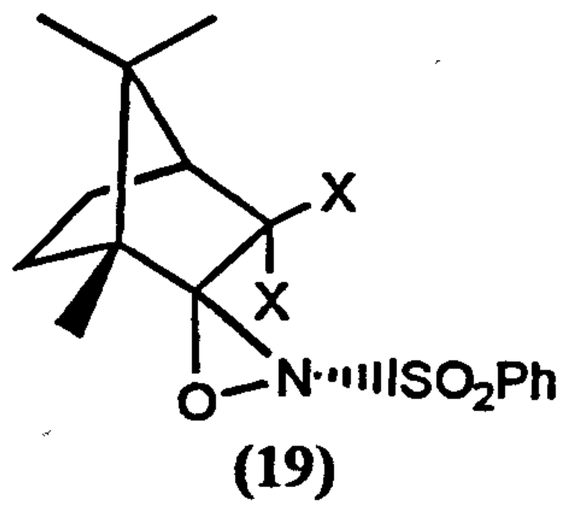
Selenuranes have recently been used for the oxidation of dialkyl sulfides to sulfoxides. These reagents give good yields for dialkyl sulfides but show little activity in the oxidation of alkyl aryl sulfides.[57]

2.4.1 Oxaziridines

Chiral oxaziridines **(18), (19)** have been prepared by Davis[58] and were first used for the asymmetric oxidation of prochiral sulfides in 1982. Since this original work, Davis has prepared many other oxaziridines and tested their potential as oxygen transfer reagents to both sulfides and olefins, with those based on camphor being the most effective. The absolute configuration of the sulfoxide produced is dependent upon that of the oxaziridine reagent itself and enantiomeric excesses of greater than 95 % have been achieved for the oxidation of many substrates. However, stoichiometric quantities of oxaziridines are required in this oxygen transfer reaction.



(18)

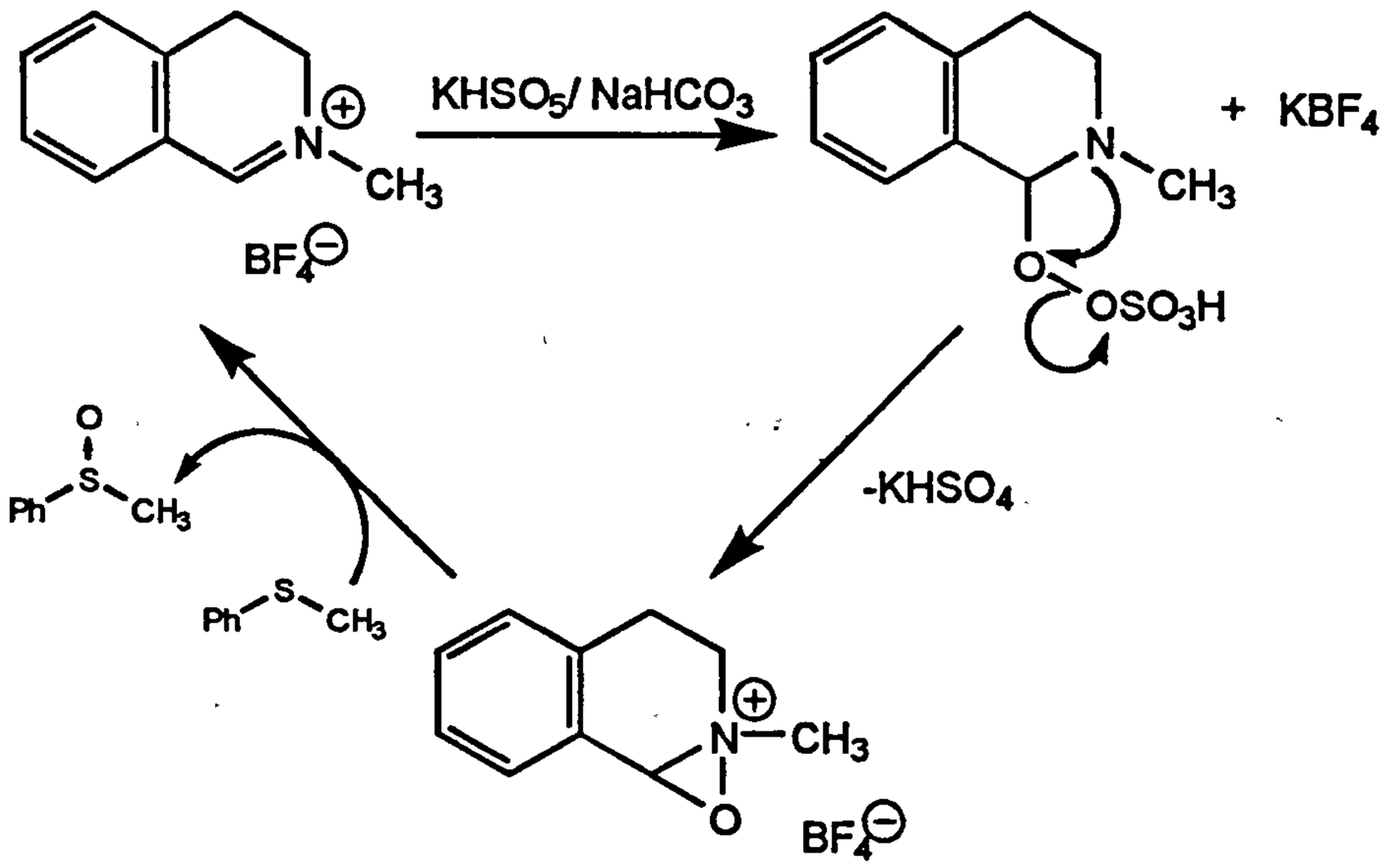


(19)

X = H, F, Cl, Br

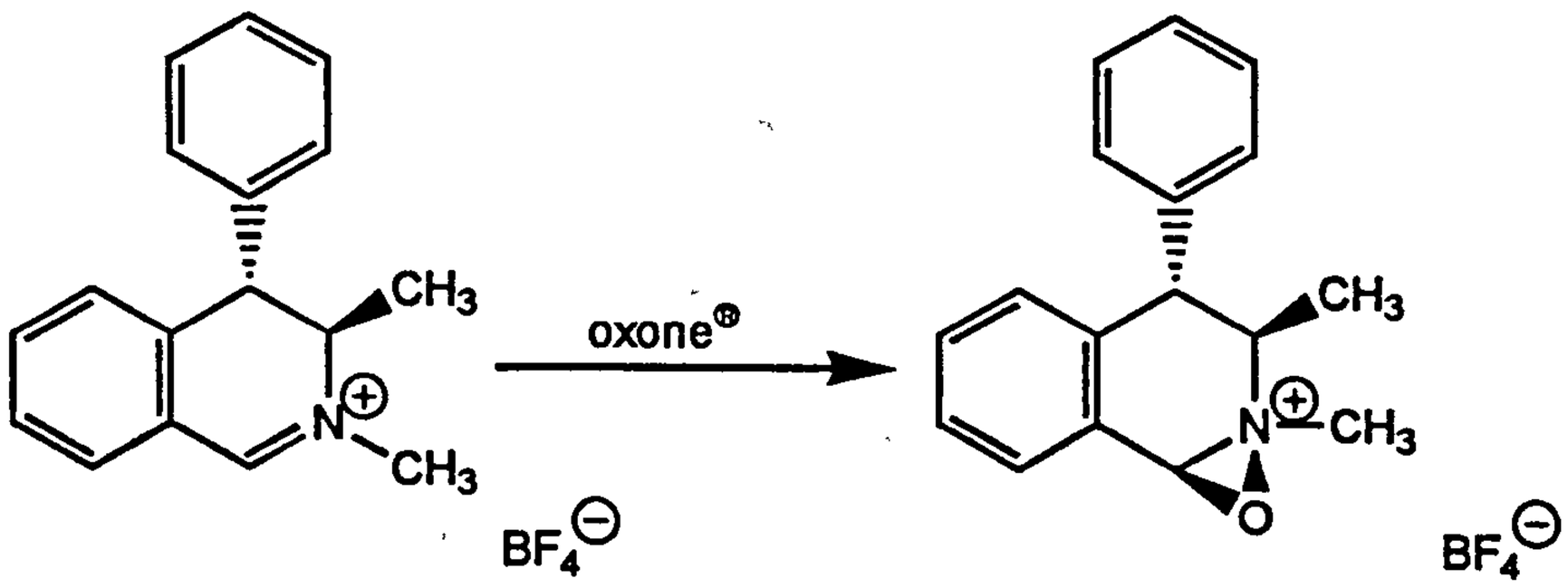
2.4.2 Oxaziridinium salts

An oxaziridinium salt was isolated by Lusinchi in 1976 and recognised as a potential oxidising agent for nucleophiles.[59] In 1987 an oxaziridinium salt was prepared from *N*-methyl-3, 4-dihydroisoquinolinium tetrafluoroborate using a peracid in the presence of sodium hydrogen carbonate.[60] The following year this oxaziridinium salt was used to effect the epoxidation of several olefins.[61] The use of Oxone® to form the oxaziridinium salt '*in situ*' enabled the catalytic oxidation of olefins[62] and sulfides (**Scheme 2.17**).[63]



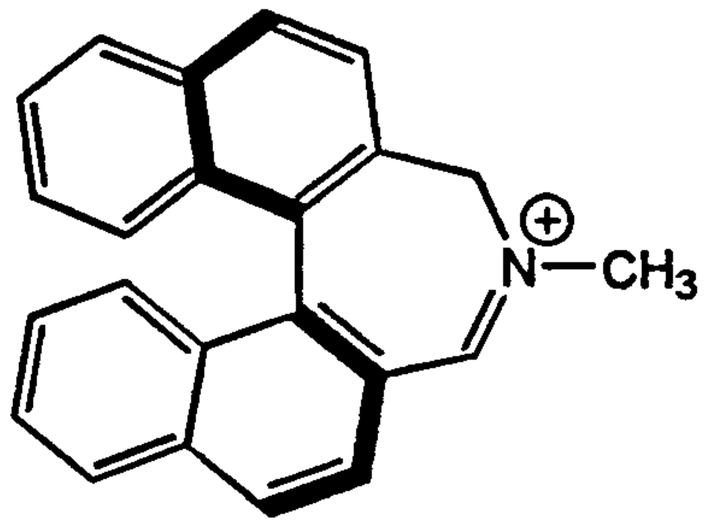
Scheme 2.17

Chiral iminium salts have been prepared and used for asymmetric sulfoxidation[64] after their transformation into oxaziridinium salts with Oxone® (**Scheme 2.18**). Using this oxaziridinium salt, methyl *p*-tolyl sulfide was oxidised with 32 % ee.



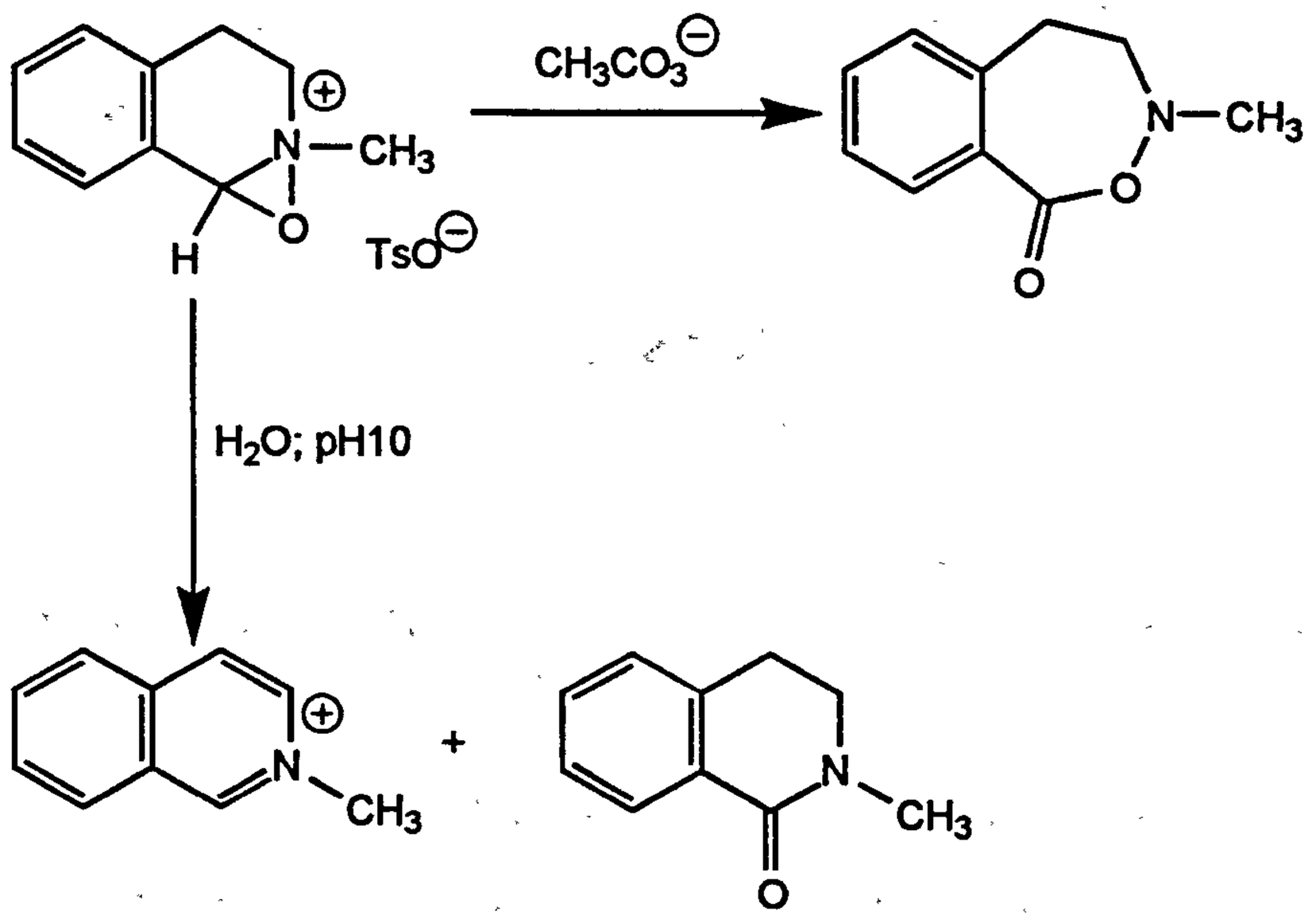
Scheme 2.18

More recent work by Aggarwal using a binaphthyl based-iminium salt[65] **(20)** has produced epoxides with moderate to good enantioselectivity using only 5 mole % of the mediator with peracetic acid as the oxidant.



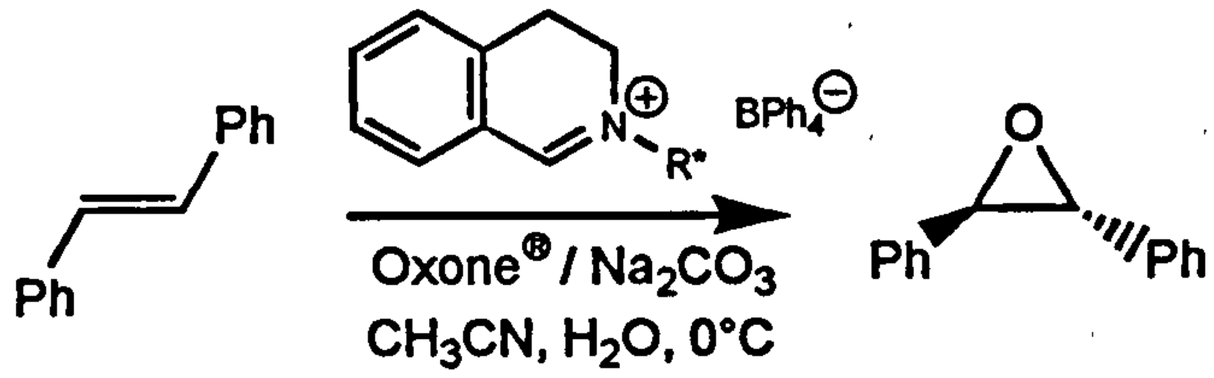
(20)

N-Methyl-3,4-dihydroisoquinolinium *p*-toluenesulfonate has been used as a catalyst for oxygen transfer from peracetic acid to an azo dye.[66] This catalytic system has been shown to undergo degradation *via* alkaline hydrolysis of oxaziridinium salt (60 %) and nucleophilic attack by peracid (**Scheme 2.19**); however, decomposition is minimised by keeping the concentration of oxaziridinium salt down e.g. by using an excess of substrate.[66]



Scheme 2.19

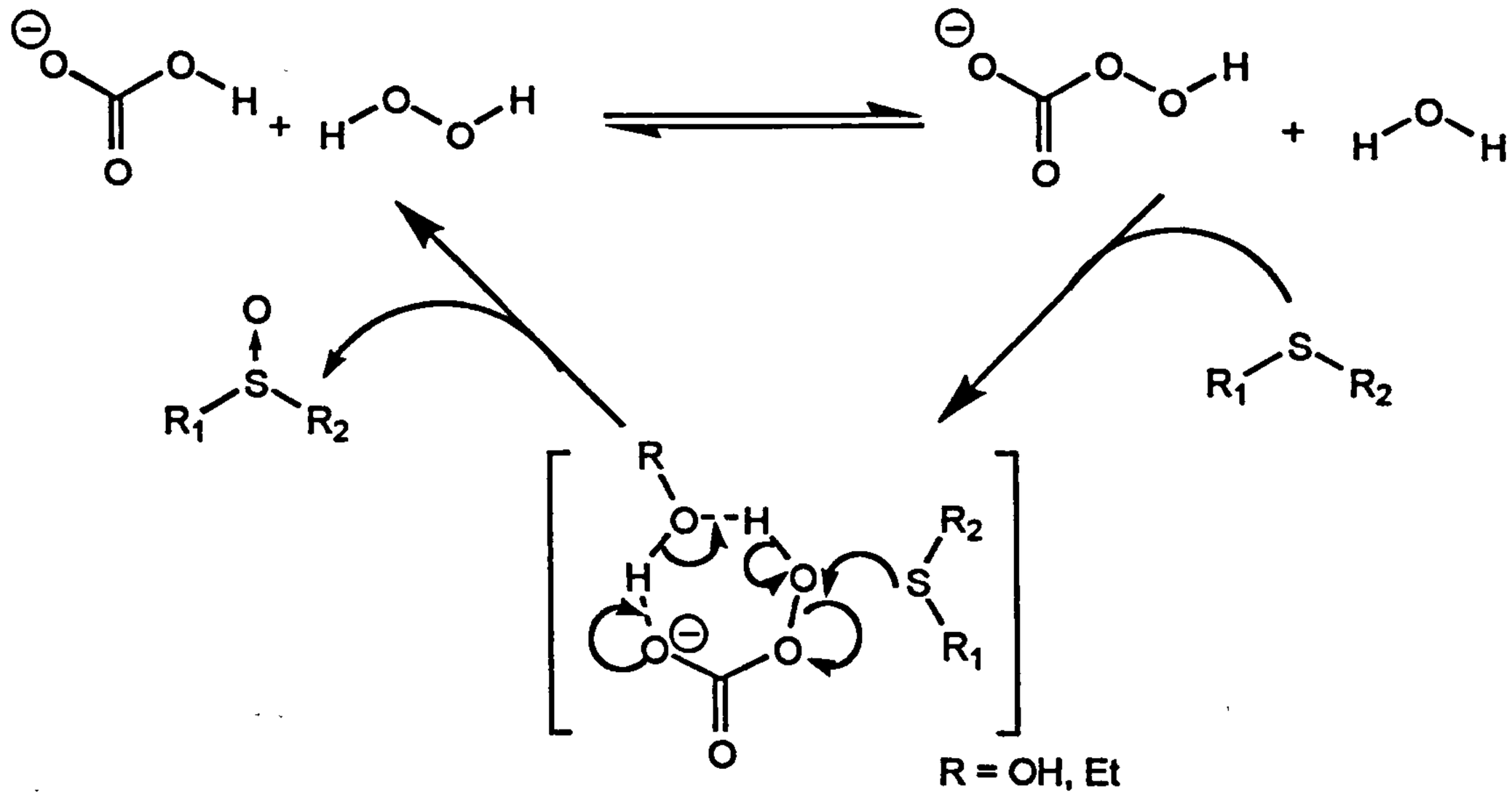
Page and Bethell have developed a system based on a chiral dihydroisoquinolinium salt and Oxone® for the asymmetric epoxidation of unfunctionalised alkenes (**Scheme 2.20**).[67] They have achieved ee's upto 73 % with yields of 78 % for the oxidation of *trans*-stilbene using only 10 mol % of catalyst.



Scheme 2.20

2.5 Novel activators of hydrogen peroxide

Richardson *et al* have recently used bicarbonate anion as an effective activator of hydrogen peroxide for the oxidation of sulfides in alcohol/ water mixtures.[68] Detailed kinetic study revealed that between pH 7 - 9 peroxymonocarbonate ion is formed from bicarbonate anion and hydrogen peroxide within a few minutes at 25°C. The rate of sulfide oxidation is increased 300-fold over that by hydrogen peroxide alone.



Scheme 2.21 Proposed mechanism for the bicarbonate catalysis of the hydrogen peroxide oxidation of sulfides

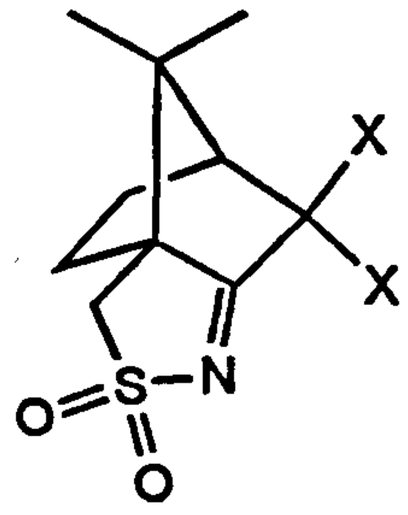
Work in Liverpool has focused on the development of highly reactive oxidants which can be generated '*in situ*' from aqueous hydrogen peroxide, for example, the Gagnieu modification of the non-catalytic Payne oxidation system with potassium carbonate and its application to the oxidation of sulfides (see above).

Imines have been used as catalytic mediators in place of the nitrile; it has been documented[69] that such compounds form oxaziridines by reaction with peracids but form hydroperoxyamines upon reaction with hydrogen peroxide. Indeed, in these reactions, such compounds mediate the oxidation of sulfides by hydrogen peroxide in

stoichiometric quantities, even though significant hydrolysis of the imine appears to take place (although formation of ketone could be attributed to attack by hydrogen peroxide on the imine and subsequent oxygen transfer to sulfide).

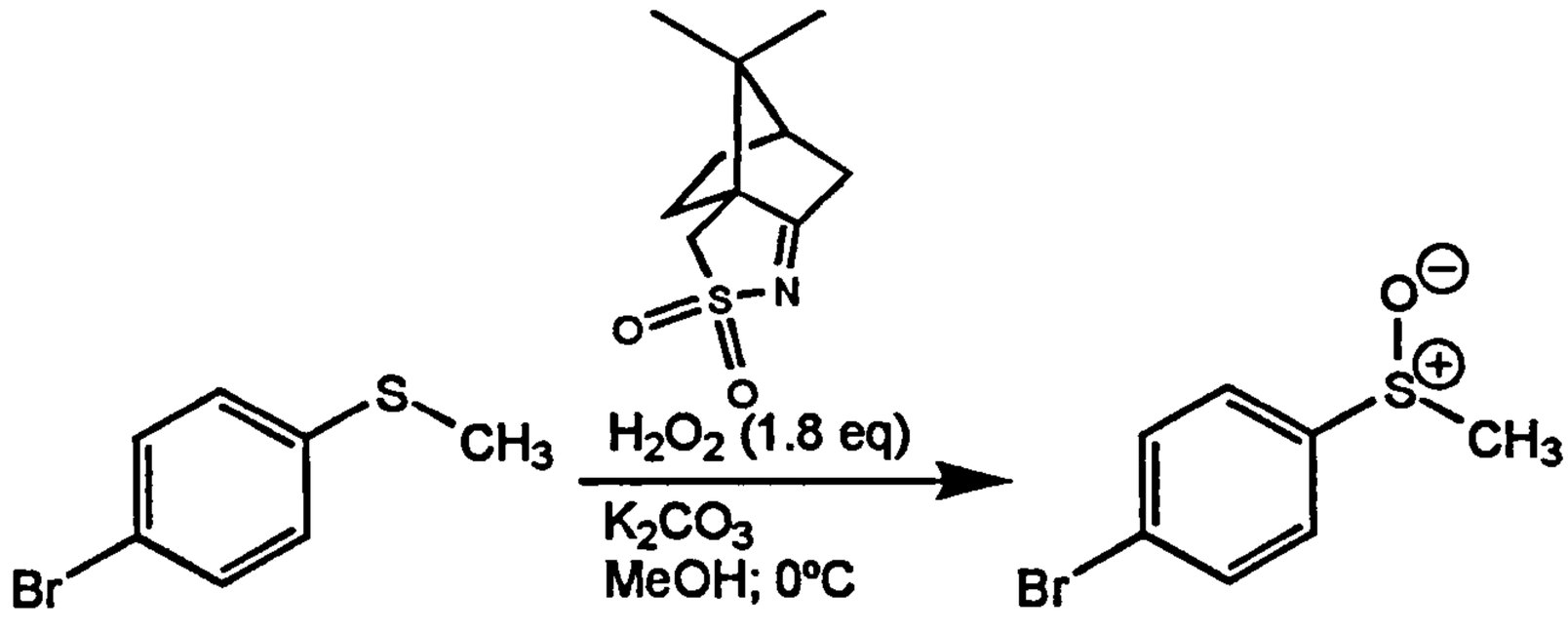
It was inferred from these initial results that suitable catalysts would have an imine moiety which was more reactive towards attack by hydrogen peroxide, but less susceptible to hydrolysis. Sulfonyl imines were identified as such catalysts; their electron withdrawing sulfonyl group makes nucleophilic attack by peroxide easier.

Sulfonyl imines based on Davis' reagent **(19)** were prepared, but gave very poor results under the reaction conditions (methanol, potassium carbonate, aqueous hydrogen peroxide).[70] This lack of reactivity was thought to be due to hydrolysis of the imine and/ or steric or electronic effects of the phenyl group. Since the resistance to hydrolysis of cyclic *N*-sulfinylimines based on camphor [camphorsulfonylimines; **(21)**] was described in the literature and that such molecules were the precursors of Davis' oxaziridine reagents **(18)** they were examined as mediators of oxygen transfer from hydrogen peroxide.



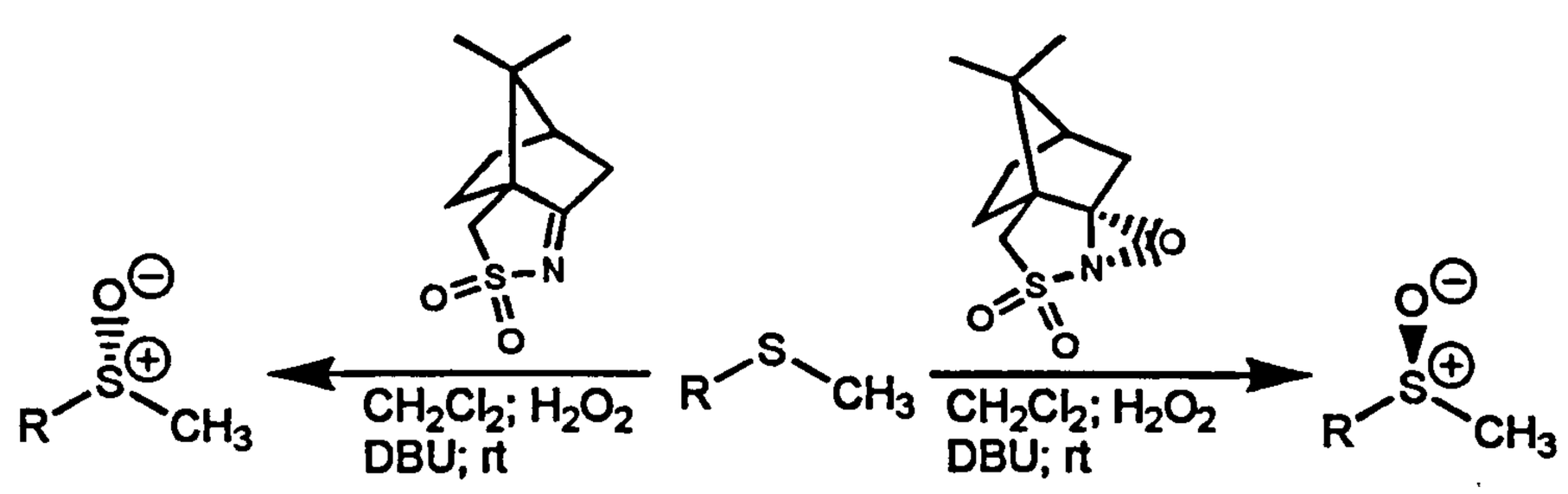
(21)

The potential of such species for oxygen transfer was soon realised when racemic camphorsulfonylimine was used to oxidize 4-bromothioanisole in 88 % yield with the recovery of 90 % of the mediator **(Scheme 2.22)**. The use of chiral camphorsulfonylimine as a sulfoxidation mediator resulted in the induction of some optical activity in the sulfoxide, which was comparable to that obtained by oxidation with the pre-formed oxaziridine. The reaction was optimised by lowering the temperature to -20°C, changing the solvent to dichloromethane, and replacing the insoluble potassium carbonate with the non-nucleophilic base DBU. After optimisation the yield of sulfoxide obtained was almost quantitative and the optical purity about 40 %.



Scheme 2.22

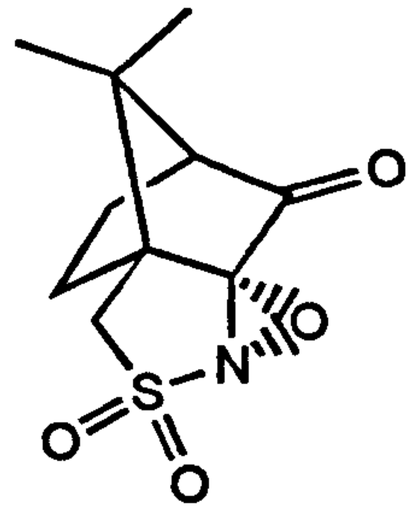
Since the dichloro oxaziridine ((**18**); X = Cl) was shown by Davis[58] to be much more enantioselective in oxidations than the unsubstituted derivative, the related imine precursor ((**21**); X = Cl) was synthesised and used in sulfoxidations with aqueous hydrogen peroxide. This mediator showed poor asymmetric induction, never matching those levels that were achieved with the pre-formed oxaziridine reagent. Furthermore, the absolute configurations of the sulfoxides produced by unsubstituted camphorsulfonylimine were opposite to those of sulfoxides produced by the oxaziridine (**Scheme 2.23**). This implies that the active species formed from hydrogen peroxide and this imine was not an oxaziridine.



R = *t*-Bu, Bn, *p*-tolyl

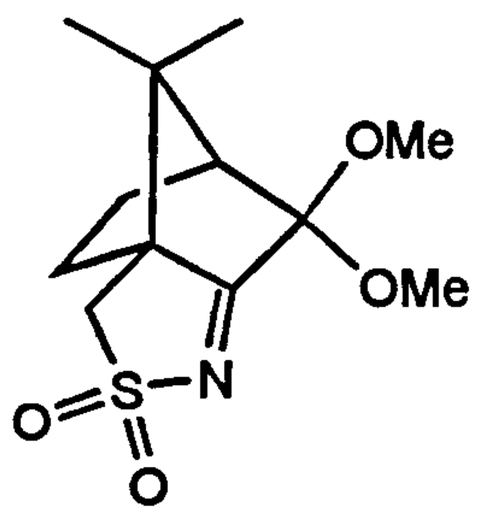
Scheme 2.23

(+)-(Oxocamphorsulfonyl) oxaziridine **(22)** was reported to be both more reactive and more selective than the simpler oxaziridine ((**18**); X = H),[71] so the imine precursor was prepared and used to oxidise thioanisole with hydrogen peroxide under the standard conditions. This imine was both less enantioselective and less reactive than (+)-(oxocamphorsulfonyl) oxaziridine **(22)**, again indicating that oxaziridine is not the active species formed by reaction of this imine with hydrogen peroxide.



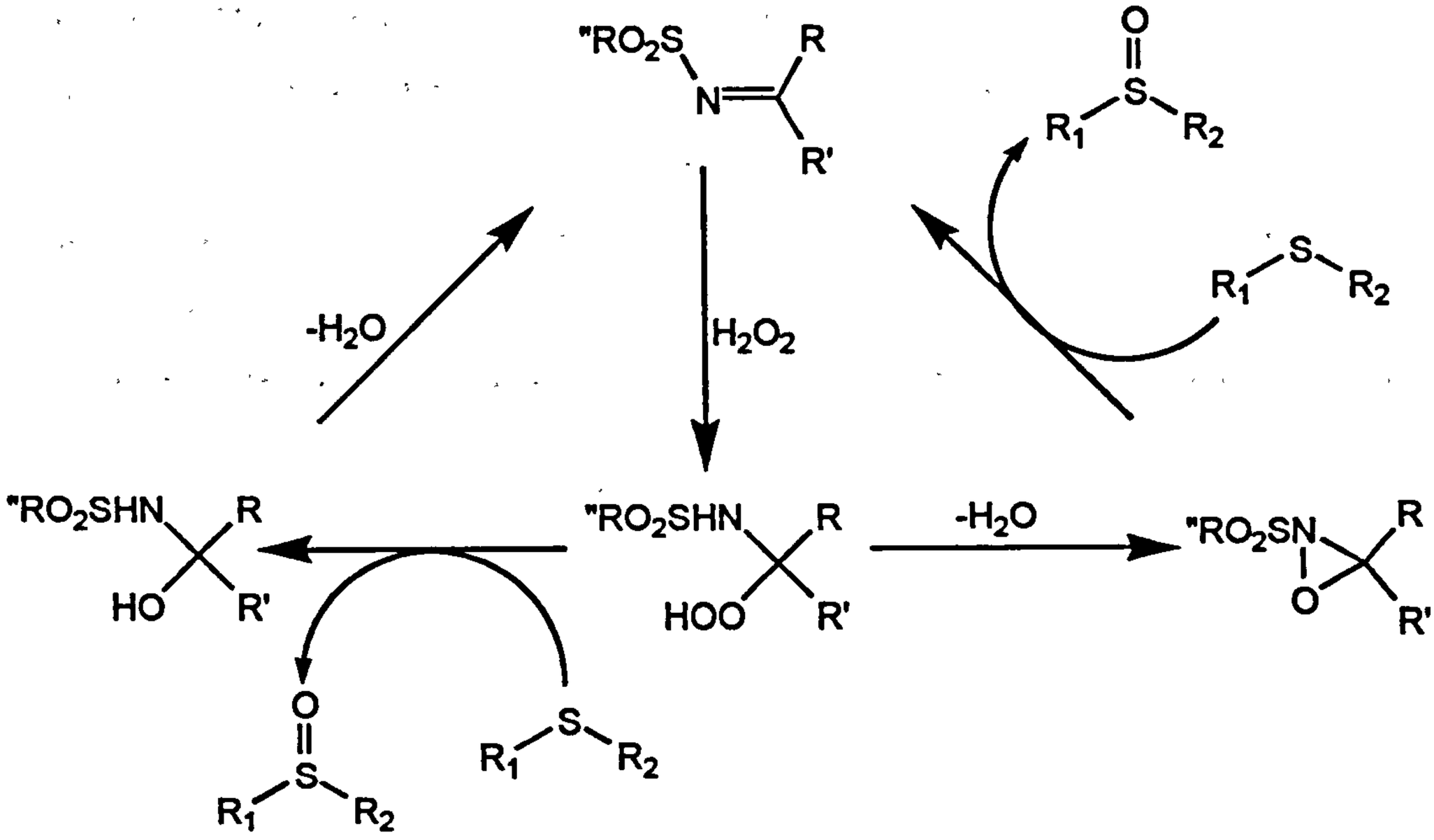
(22)

(+)-[(8,8-Dimethoxycamphoryl)sulfonyl] imine **(23)** and its oxaziridine had been prepared by Davis but not used in sulfoxidations. When this imine was employed as an oxygen transfer mediator it gave the highest levels of asymmetric induction so far, furthermore it gave the best results for non-aryl alkyl sulfides. Use of the oxaziridine to oxidise the same substrates gave results which agreed in terms of yield, asymmetric induction and absolute configuration and implied that the active species formed '*in situ*' from (+)-[(8,8-dimethoxycamphoryl)sulfonyl] imine and hydrogen peroxide is the oxaziridine.



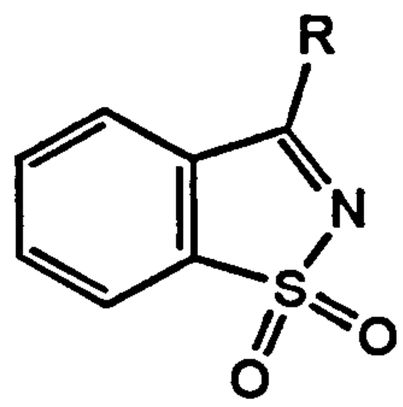
(23)

All of the (camphorsulfonyl)imine derivatives above have been shown to form the corresponding oxaziridine on treatment with aqueous hydrogen peroxide and potassium carbonate in methanol.[72] However, Hammett plots showing the relative reactivities of 4-substituted thioanisoles[73] with both camphorsulfonylimines and the corresponding oxaziridines are similar for X = OMe, but different for X = H. These results and those presented above imply that there are two competing pathways available for the imine after attack by hydrogen peroxide **(Scheme 2.24)**.



Scheme 2.24

Recent work has caused debate over the mechanism of the *O*-transfer step from oxaziridines to substrates. Theoretical studies suggest that this is a concerted S_N2-type reaction for neutral substrates[74] (e.g. sulfides, olefins) with no intermediate; whereas other work[75] has suggested the formation of a zwitterionic intermediate for the reaction of the Davis reagent with substituted indoles. The participation of a discrete ionic intermediate is also inferred from semi-empirical calculations (PM3 parameterization)[73] for the reaction of thioanisole with (camphorsulfonyl) oxaziridine.



R = Cl, OEt, Me, *i*-Pr, *n*-Bu, *s*-Bu, *t*-Bu, Ph

(24)

Pseudo-saccharin derivatives (3-substituted-1,2-benzisothiazole-1,1-dioxides; **(24)**) have been synthesised and used stoichiometrically to oxidise methyl *p*-tolyl sulfide (**Table 2.13**). The best mediator was found to be the 3-*tert*-butyl-substituted compound, which produced a yield of 84 % of sulfoxide when present in only 10 mole %. Detailed study revealed that isopropyl, *n*- and *sec*-butyl-compounds were deprotonated at the α-carbon atom of the alkyl substituent to give inactive

compounds. The existence of these anions was confirmed by capturing them with methyl iodide (**Scheme 2.25**).[76] The oxaziridine derived from 3-*tert*-butyl-saccharin has been prepared from the corresponding imine using *m*CPBA in the presence of potassium carbonate, as first described by Davis,[77, 78] who used chiral oxaziridines for epoxidation.[79]

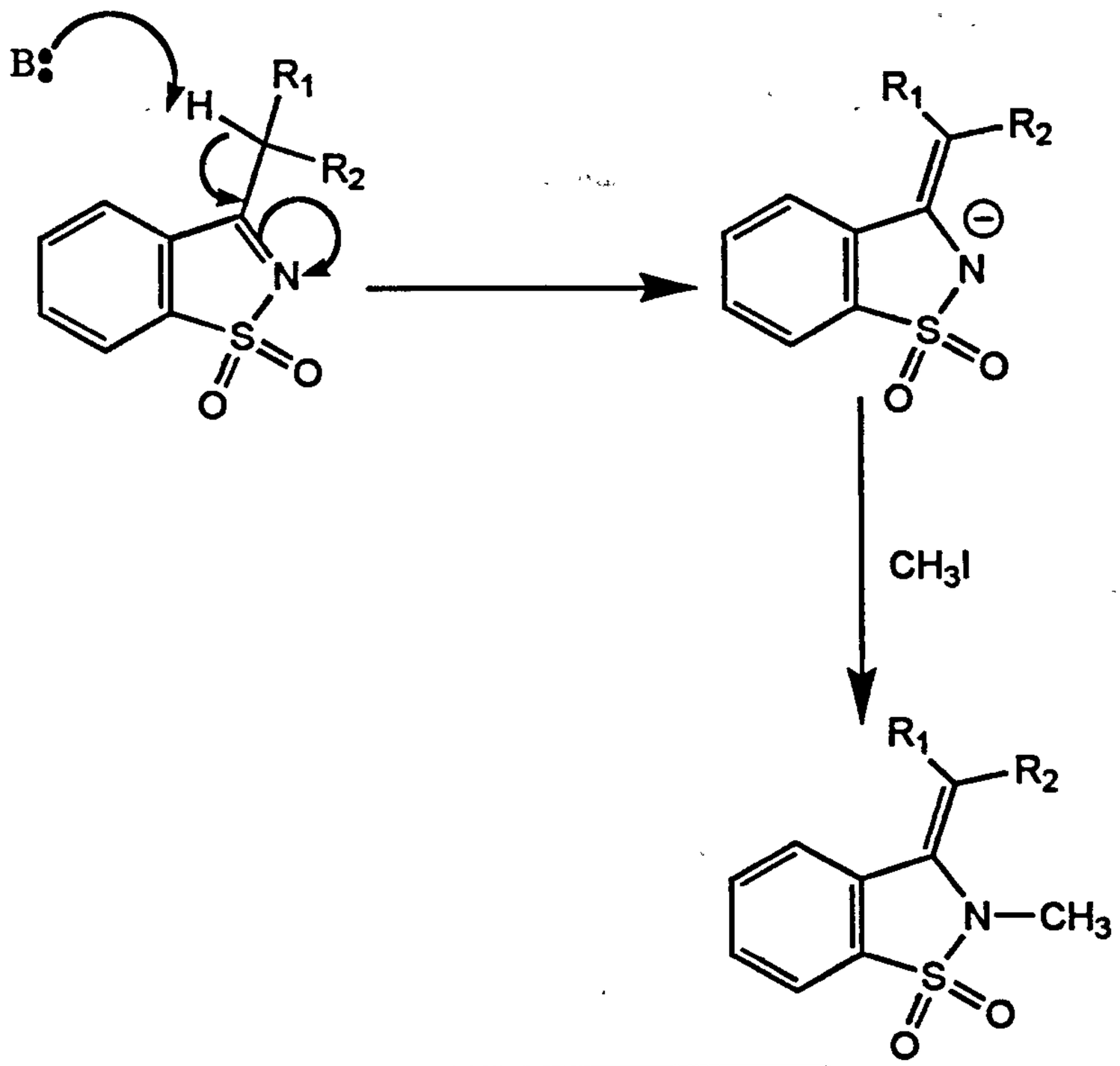
Table 2.13 Oxidation of methyl *p*-tolyl sulfide mediated by pseudosaccharin derivatives

R	Time	Temp (°C)	Conditions[a]	Yield (%)
Cl	2 d	-25	B	11
OEt	2 d	-25	A	13
OEt	3 d	-25	B	13
Me	1 d	25	A	63
i-Pr	2 h	0	B	34
n-Bu	3 d	0	A	27
n-Bu	2 h	25	A	55
n-Bu	2 h	0	B	13
n-Bu	5 d	0	B	58
s-Bu	29 h	-10	B	80
s-Bu	2 h	0	B	80
s-Bu	2 h	20	B	5
s-Bu	31.5 h	20	B	43
t-Bu	2 d	-50	B	33
t-Bu	2 h	0	B	58
t-Bu	1.45 h	20	B	100
t-Bu[b]	8 d	25	B	84
Ph	2 h	0	B	30

[a] Conditions: A H_2O_2; K_2CO_3; MeOH
B H_2O_2; DBU; DCM

[b] 10 mol % used

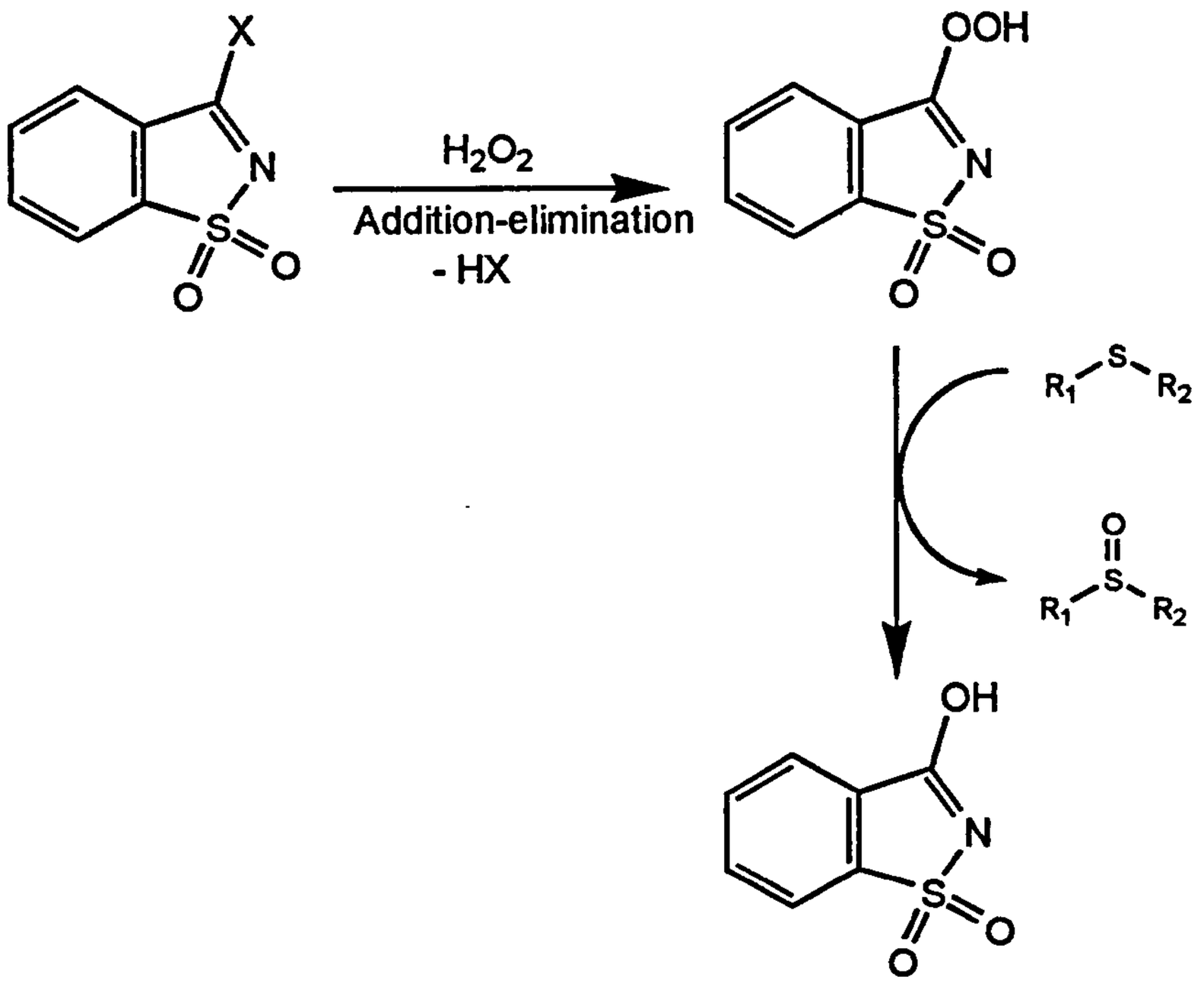
Base and peroxide were used in excess



Compound	R_1	R_2
3-*n*-Bu	n-Pr	H
3-*s*-Bu	Et	Me

Scheme 2.25

Pseudo-saccharin derivatives substituted in the 2-position with leaving groups **((24)**; R = Cl, OEt) were expected to form peroxyimidic acids **(14)** '*in situ*' with hydrogen peroxide (**Scheme 2.26**; reminiscent of the earlier nitrile mediated Payne-type oxidations). However, such species oxidised methyl *p*-tolyl sulfide in low yield with aqueous hydrogen peroxide. When water was omitted from the reaction and anhydrous urea hydroperoxide was used as the oxidant, the sulfide was totally converted to sulfoxide (63 %) and sulfone (30 %).[70] The sulfone formation suggests that there is a very reactive oxidant present, but, surprisingly, the same catalytic system failed to oxidise styrene at all.



Scheme 2.26

Alkylation of the pseudo-saccharin-derivatives has been attempted in order to prepare sulfonyliminium salts that would be more active with regard to nucleophilic addition. Such molecules are expected to form α-hydroperoxy amines upon reaction with hydrogen peroxide, although oxaziridinium salt formation is possible, but unlikely due to the loss of hydroxide ion that is required. All attempts at alkylation of camphorsulfonylimines **(18)** and pseudosaccharin derivatives **(24)** failed.

2.6 Conclusions

Many different reagents have been used to activate hydrogen peroxide towards the oxidation of sulfides: acylating agents (that generate peroxycarboxylic acids), transition metal complexes, carbonyl compounds (that form α-hydroxyhydroperoxides), nitriles (that form peroxyimidic acids) and imines (that form either hydroperoxyamines or oxaziridines).

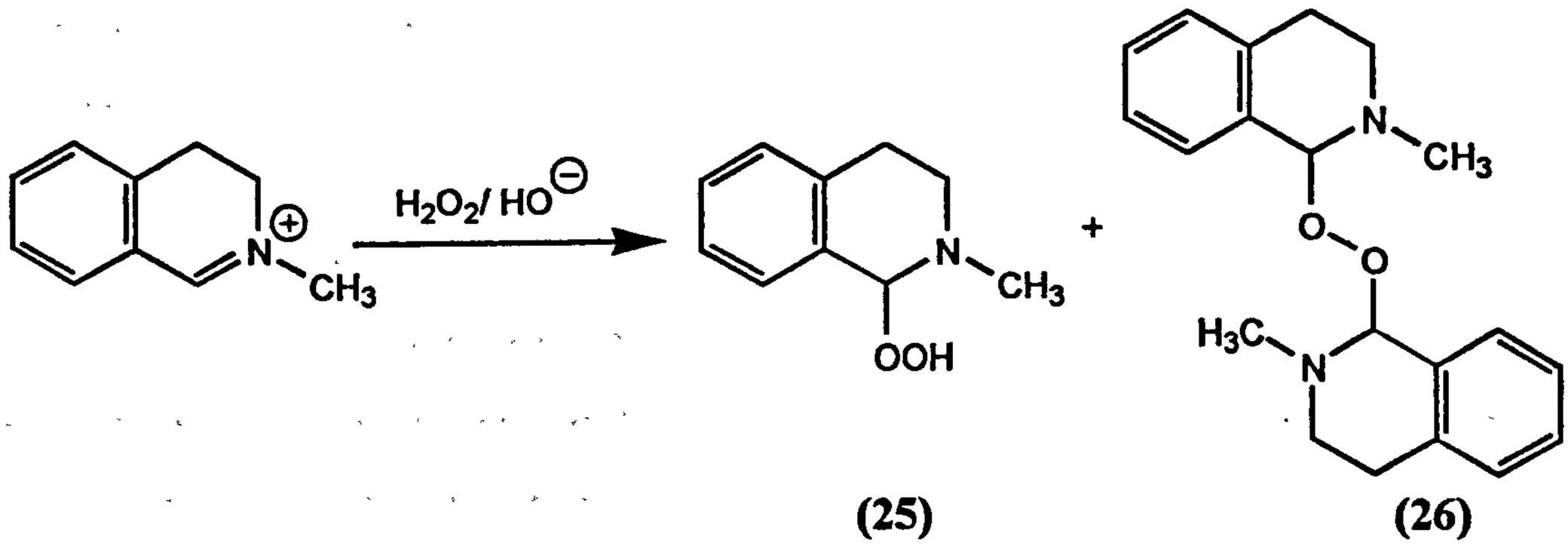
Unfortunately the camphorsulfonylimine catalytic systems developed need stoichiometric quantities of imine to catalyse the oxidation of sulfides at a reasonable rate. Also sub-zero temperatures are necessary for good enantioselection to be achieved and, as such, the oxidation occurs rather slowly. The temperature range for laundry bleaching is 21-45°C[80] and an ideal mediator should work both quickly and selectively within this range. For hard surface cleaning, selectivity is less important and it is carried out at ambient temperatures, generally between 5-30°C. Furthermore, these compounds are not soluble in water and would therefore be unsuitable for either fabric bleaching or hard-surface cleaning.

Activators that have been developed so far have one (or more) of several problems: they are not reactive enough and they require the use of one equivalent of mediator, they are not selective, they are not water-soluble, they are susceptible to hydrolysis, or they involve the use of toxic metallic compounds and so generate unacceptable waste streams.

Improved mediators will react with hydrogen peroxide to form a more reactive and more selective oxygen transfer agent. They will be water-soluble and active in sub-stoichiometric quantities i.e. catalytic. The main problem is to increase the relative rate of formation of the oxygen transfer intermediate without increasing the susceptibility of the mediator to hydrolysis. However, in the context of laundry bleaching, hydrolysis can be a good way to deactivate the mediator at the end of the wash cycle, providing the products are water-soluble and non-toxic.

Unilever has used an iminium salt, *N*-methyl-3, 4-dihydroisoquinolinium *p*-toluenesulfonate, in conjunction with hydrogen peroxide for hard-surface cleaning applications. This mixture has a better cleaning performance than hydrogen peroxide alone and one that approaches the performance of sodium hypochlorite. The mixture is both environmentally acceptable and safe to mix with acid. Furthermore, it has a low inherent odour and is thus easily perfumed. A prototype WC formulation has been developed that fulfills disinfecting criteria (European Suspension Test). The

active oxygen transfer agent is unknown, although it is thought to be a hydroperoxyamine or an oxaziridinium salt. The hydroperoxyamine species **(25)** and a dimeric dialkyl hydroperoxy derivative **(26)** have been observed by ^{1}H NMR in solutions of the oxaziridinium salt in alkaline hydrogen peroxide **(Scheme 2.27)**.



(25) **(26)**

Scheme 2.27

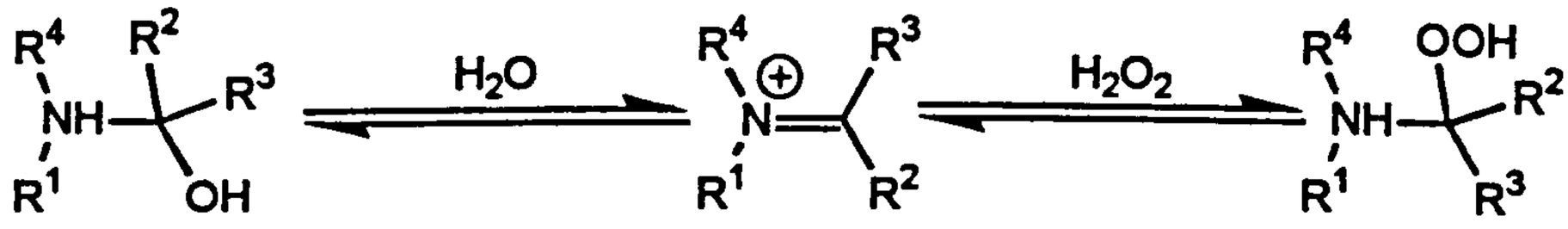
2.7 The present investigation

The present investigation is concerned with the development of novel compounds that activate hydrogen peroxide (an environmentally friendly oxidant) towards electrophilic oxidations. Such an activator is required in the cleaning industry because of concerns about sodium hypochlorite, which is currently used for such applications.

The aim of this project is the discovery and development of novel compounds for the transfer of oxygen from hydrogen peroxide to selected organic molecules, chosen to model common classes of household stains. Suitable molecules will form reactive and selective oxygen transfer agents upon reaction with hydrogen peroxide.

Obvious candidates for improved catalysts are molecules containing an iminium moiety because some iminium salts have been shown to form oxaziridinium salts '*in situ*' upon reaction with Oxone® or peroxycarboxylic acids. Such compounds should form active oxygen transfer agents upon reaction with hydrogen peroxide; whether this intermediate is a hydroperoxyamine or an oxaziridinium salt, it should be highly reactive towards nucleophilic substrates.

The fundamental challenge in this area is to develop mediators with improved activity towards peroxide addition without increasing the susceptibility of the molecule to hydrolysis either in solution or on the 'shelf' **(Scheme 2.28)**. It is usually the case that faster perhydrolysis in solution is accompanied by both faster 'in pack' hydrolysis and 'in pack' perhydrolysis.

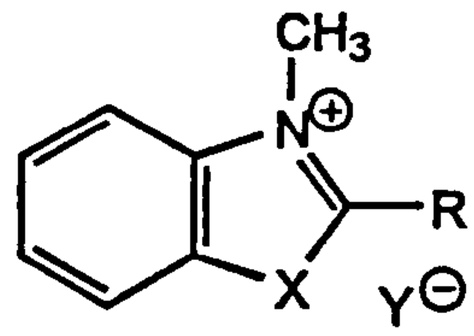


Scheme 2.28

In the light of these observations, possible catalytic mediators investigated initially are those based on benzoxazolium/ benzothiazolium derivatives and indoleninium species **(27)**. The model reaction we have chosen to assess the mediators is the oxidation of sulfides to sulfoxides because this reaction can be both carried out and monitored easily; selectivity can be measured by any over-oxidation to sulfone as this is easily detected.

Appraisal studies have been carried out to assess the potential mediators for hard surface cleaning applications in conjunction with hydrogen peroxide. This

appraisal involves monitoring the ability of these systems to remove two types of model soil: curcumin-oil on formica tiles and mould paste on unglazed kitchen tiles.



R = alkyl, aryl
X = O, S, CR_2
Y = BF_4, TsO

(27)

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Chapter 3

The Synthesis Of Iminium Salts

3.1 Introduction

Initial screening of the activity of the mediators was carried out by monitoring their ability to oxidise sulfides to sulfoxides. This reaction was chosen because it can be both carried out and monitored easily; over oxidation (to sulfone) is easily detected and this provides a good measure of selectivity.

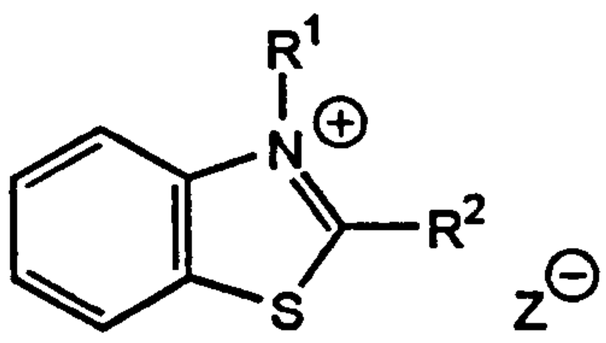
There have been many attempts to develop novel mediators capable of catalytic asymmetric oxygen transfer from hydrogen peroxide to organic sulfides because of the importance of chiral sulfoxides in organic synthesis, where they are employed as synthons, auxiliaries and ligands.[1] Furthermore, the synthesis of optically-active sulfoxides has often proved difficult.

The growing importance of chiral sulfoxides stems from the fact that homochiral sulfoxides are able to control the formation of new stereogenic centres before being removed under mild conditions (e.g. by reduction, β-elimination, Pummerer-type reactions[2], retro Diels-Alder reaction[3]). There are many different procedures for the preparation of sulfoxides,[4] but there are only a small number of genuinely convenient, generally applicable methods, perhaps indicating the complexity of this apparently simple reaction.

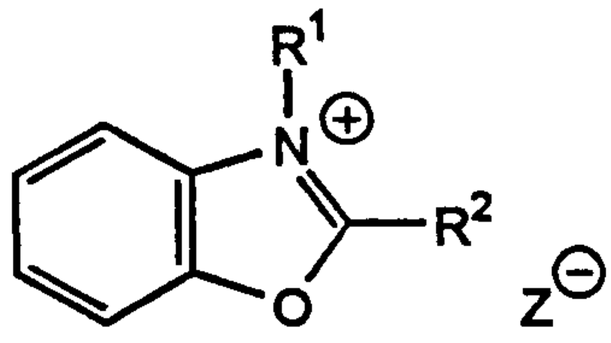
Molecules investigated during this study contained iminium moieties that were expected to be active for the formation of hydrogen peroxide adducts. These were anticipated to be capable of *O*-transfer to sulfides and, it was hoped, regeneration of the iminium salt and hence turnover and catalysis.

As discussed in chapter 2, sulfonyl imines have been previously developed in our laboratories and used for *O*-transfer from hydrogen peroxide to organic sulfides. Although catalytic, stoichiometric quantities of these mediators are required to catalyse sulfide oxidation at a reasonable rate. Furthermore, the oxidation occurs rather slowly at the sub-zero temperatures necessary for good enantioselection to be achieved. Increasing the activity of the sulfonylimines has been attempted by alkylation of the nitrogen atom, but this failed for both camphorsulfonylimines **(21)** and pseudo-saccharin derivatives **(24)**.

Compounds that are structurally similar to 3-alkyl-pseudo-saccharin derivatives are benzothiazolium **(28)** and benzoxazolium **(29)** salts, possessing an iminium moiety and a further heteroatom in the ring. These molecules should form α-hydroperoxy amines upon reaction with hydrogen peroxide, and then, possibly, an oxaziridinium salt.



(28)



(29)

R^1 = Me, Et
R^2 = H, Me, Ph, ^{t}Bu, Cl
Z = TsO, BF_4

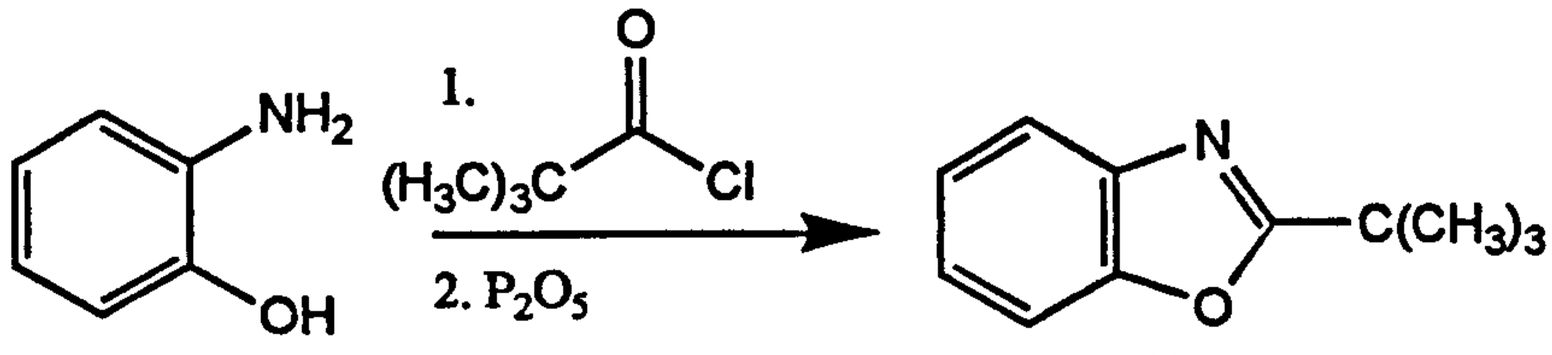
This chapter will discuss the synthesis of the iminium salts and their precursors. Chapter 4 is concerned with screening the salts for *O*-transfer activity; this is achieved by testing their ability to oxidise thioanisole in conjunction with hydrogen peroxide. The mechanism of the oxidations is investigated in chapter 5 by firstly looking at the effect of concentrations upon the rate and then by carrying out competitive oxidations of *p*-substituted thioanisoles.

3.2 Synthesis of benzoxazolium and benzothiazolium salts

3.2.1 Preparation of benzoxazoles

The most popular synthesis of benzoxazoles is by the reaction of *o*-aminophenols with a carboxylic acid or derivative (e.g. anhydride or chloride).[5]

2-*t*-Butyl benzoxazole **(30)** was prepared by *N*-acylation of *o*-aminophenol and subsequent dehydration with phosphorous pentoxide **(Scheme 3.1)**.[6] Very little of the diacylated product, reported by Theilacker in 1939,[7] was observed and, after extraction into hexane, simple flash column chromatography gave the product as a red oil in 45 % yield.

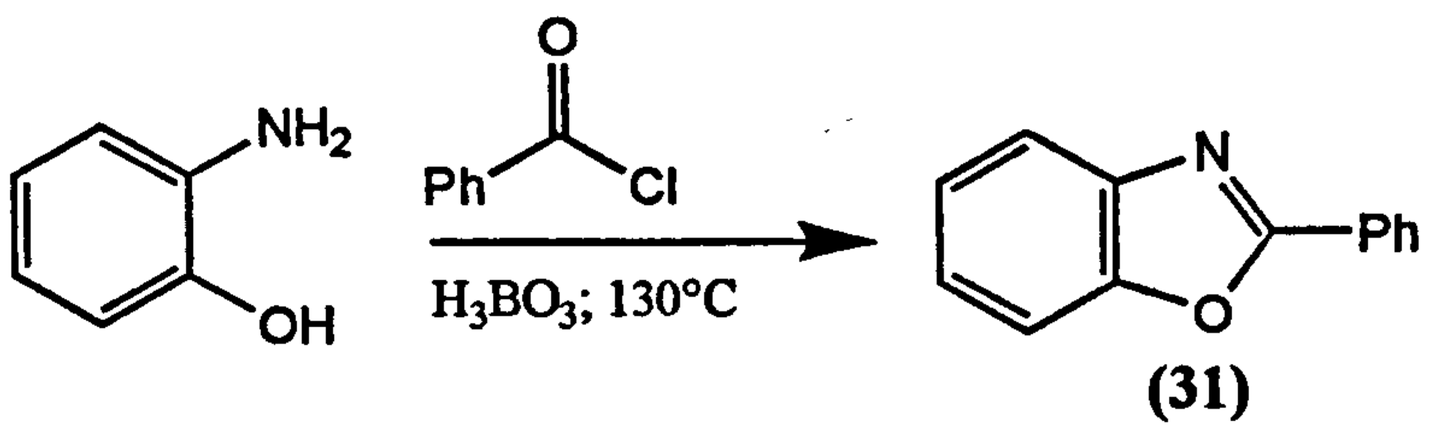


(30)

Scheme 3.1

2-Phenyl benzoxazole **(31)** was not produced in good yield by *N*-benzoylation and dehydration of *o*-aminophenol as above, and so a different procedure was followed. 2-Phenyl benzoxazole was prepared by the boric acid catalysed condensation of *o*-aminophenol with benzoyl chloride according to the method of Kanaoka **(Scheme 3.2)**.[8] It was separated from benzoic acid (formed by

the competing hydrolysis of benzoyl chloride) by flash column chromatography, affording **(31)** in 62 % yield.



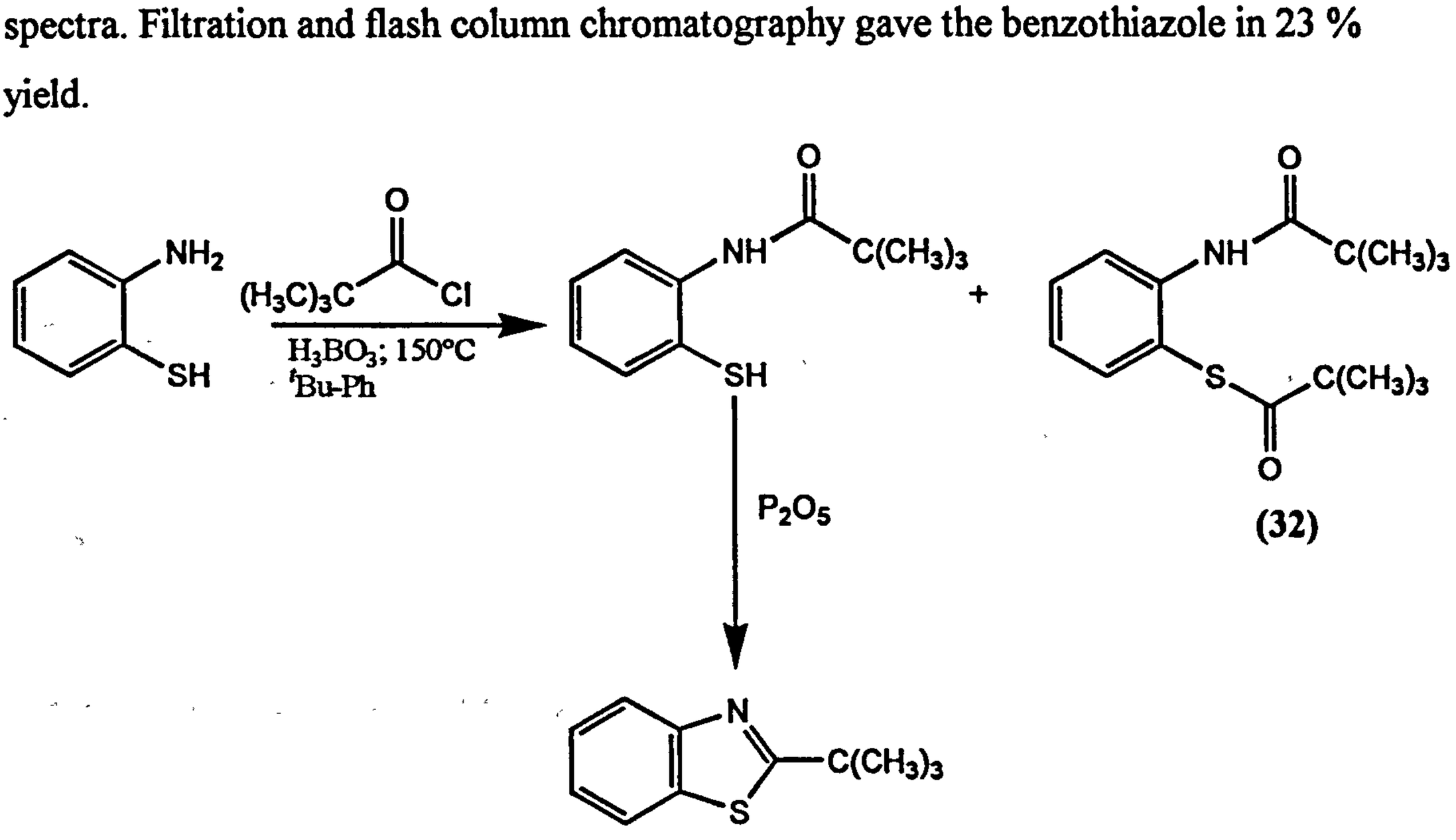
(31)

Scheme 3.2

2-Methylbenzoxazole and benzoxazole were commercially available compounds and were used as supplied.

3.2.2 Preparation of benzothiazoles

2-*t*-Butyl benzothiazole **(33)** was prepared by heating *o*-aminothiophenol with trimethylacetyl chloride and subsequent dehydration with phosphorous pentoxide (**Scheme 3.3**).[8] A small amount of the diacylated product **(32)** was observed as a precipitate (5 %); this was identified from its ^{1}H NMR and mass spectra. Filtration and flash column chromatography gave the benzothiazole in 23 % yield.



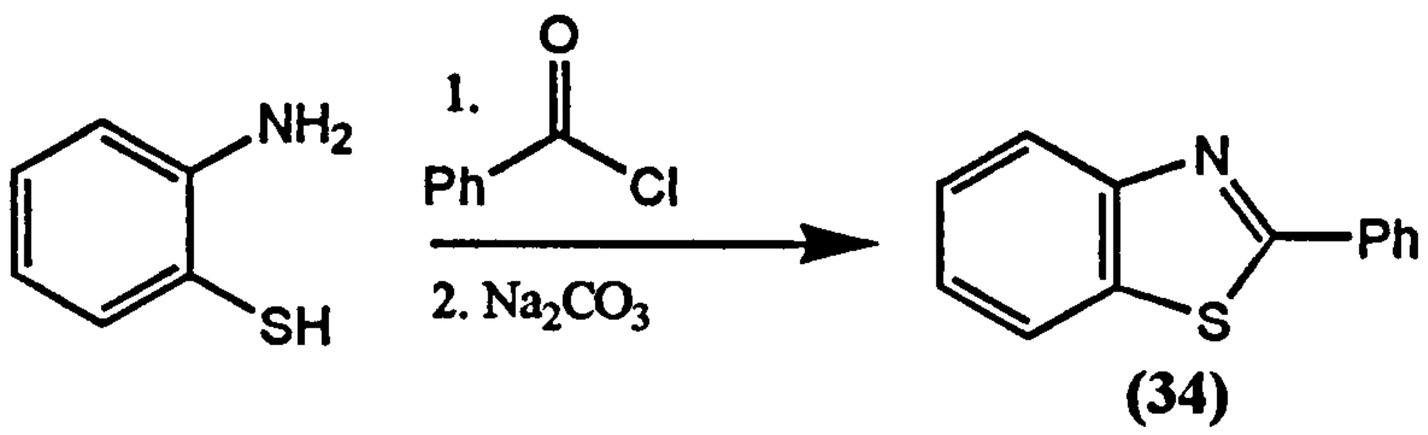
(32)

(33)

Scheme 3.3

2-Phenyl benzothiazole **(34)** was synthesised by the reaction of *o*-aminothiophenol with benzoyl chloride in chloroform cooled below 0°C. After

boiling the mixture with aqueous sodium carbonate solution, simple extraction into diethyl ether gave the product in 85 % **((34); Scheme 3.4)**.



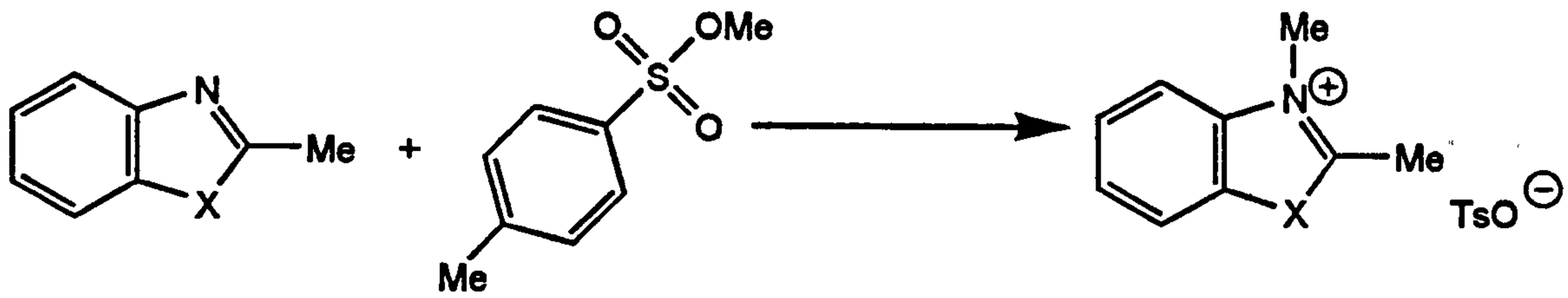
(34)

Scheme 3.4

2-Methylbenzothiazole and benzothiazole were commercially available compounds and were used without purification.

3.2.3 *N*-Methylation by methyl tosylate

2,3-Dimethylbenzoxazolium tosylate and 2,3-dimethylbenzothiazolium tosylate were prepared by *N*-methylation of the corresponding benzoxazole/ benzothiazole **(Scheme 3.5)**.[9] The 2-methylbenzoxazole/ benzothiazole was stirred for 24 hours at room temperature with methyl tosylate in the absence of solvent to give the tosylate salt, which was crystallised by the slow addition of diethyl ether to an acetone solution of the crude product. The mother liquor could be concentrated and stirred again to give more product after a further period. Yields were 60 and 77 % respectively.



X = O, S

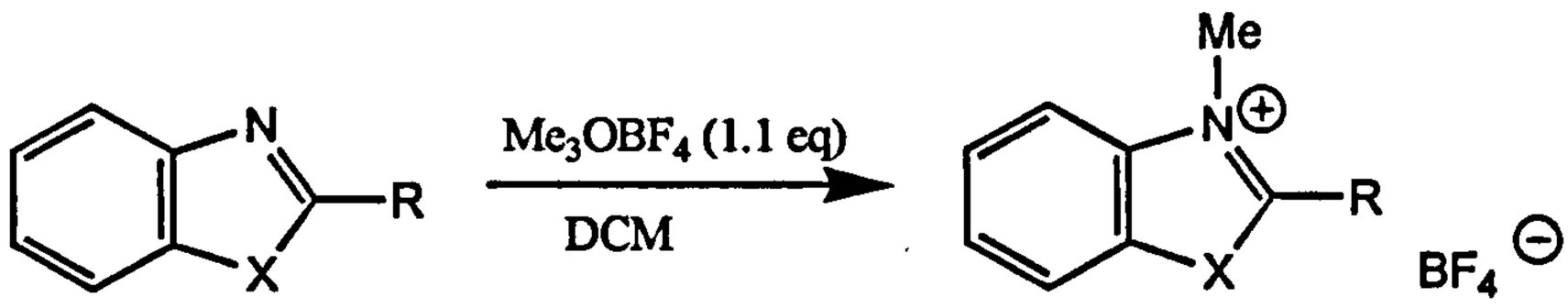
Scheme 3.5

3.2.4 *N*-Methylation by Meerwein's reagent[10]

The synthesis of benzoxazolium tetrafluoroborate salts was carried out according to the method of Quast and Hünig.[11] Reaction of Meerwein's reagent[12] with 2-substituted benzoxazoles gives the corresponding *N*-methyl tetrafluoroborate salt in good yield with the only additional product being the volatile dimethyl ether. *N*-Methylation by methyl tosylate has been reported for some of these benzoxazoles, but the yields were not so good.[9] This method was used for the synthesis of 2-substituted benzoxazolium and benzothiazolium salts which either did not react with

methyl tosylate under ambient conditions because of their bulky 2-substituents (R = *t*-Bu, Ph) or for the synthesis of unstable salts (R = H) which hydrolysed under the longer reaction times needed for reaction with methyl tosylate.

Synthetic procedures for the synthesis of 2-substituted benzoxazolium and benzothiazolium tetrafluoroaborate salts are shown in **Scheme 3.6**. The benzoxazolium **(35)**, **(36)** and **(37)** and benzothiazolium salts **(38)**, **(39)** and **(40)** were prepared in good yields and all gave satisfactory ^{1}H NMR spectra and accurate mass data which are shown in **Table 3.1**; unfortunately all the salts contain too much fluorine for elemental analysis.



X = O, S
R = H, Ph, *t*-Bu

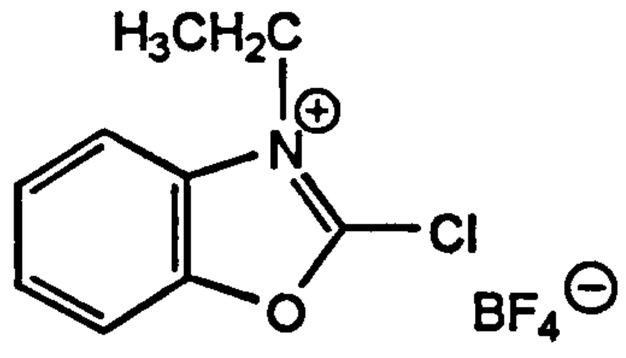
Scheme 3.6

Table 3.1 Data for 2-substituted benzoxazolium and benzothiazolium tetrafluoroborate salts

Compound	R	Yield (%)	Accurate mass found	Accurate mass required	mp (°C)	Lit. mp (°C)
(35)	(H)	81	134.06102	134.06059	147-9	-
(36)	(Ph)	88	210.09194	210.09189	168-170	-
(37)	(*t*-Bu)	93	190.12282	190.12319.	163-4	-
(38)	(H)	99	150.03791	150.03775	119-120	118.5-119.5[10]
(39)	(Ph)	83	226.06921	226.06905	197-9	-
(40)	(*t*-Bu)	94	206.10045	206.10035	218-9	218-220[11]

Although many of the benzoxazolium cations have been prepared, literature data for the melting points of some compounds could not be found because the anions were different.

2-Chloro-3-ethylbenzoxazolium tetrafluoroborate **(41)** was a commercially available compound and was used as supplied.

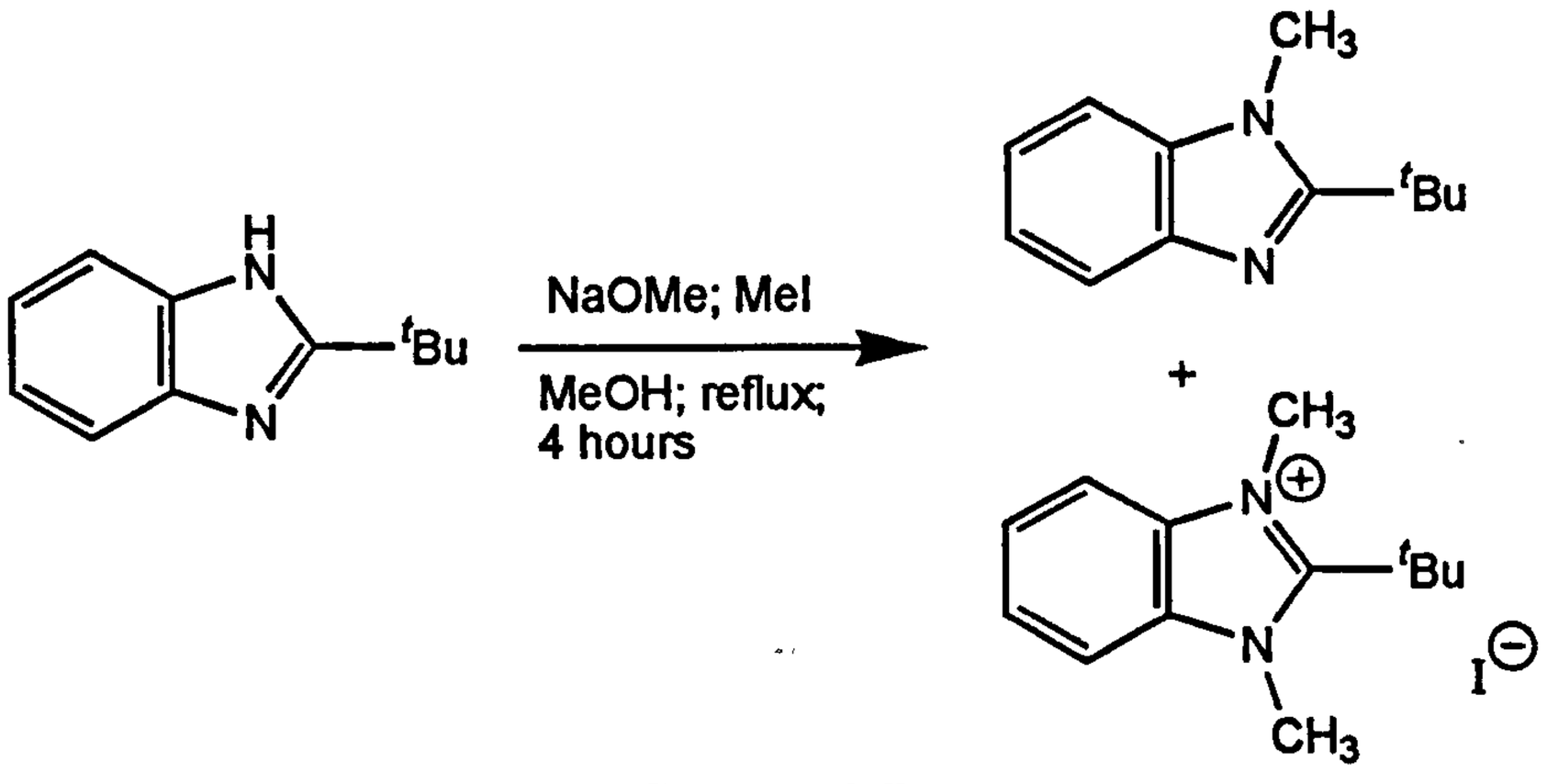


(41)

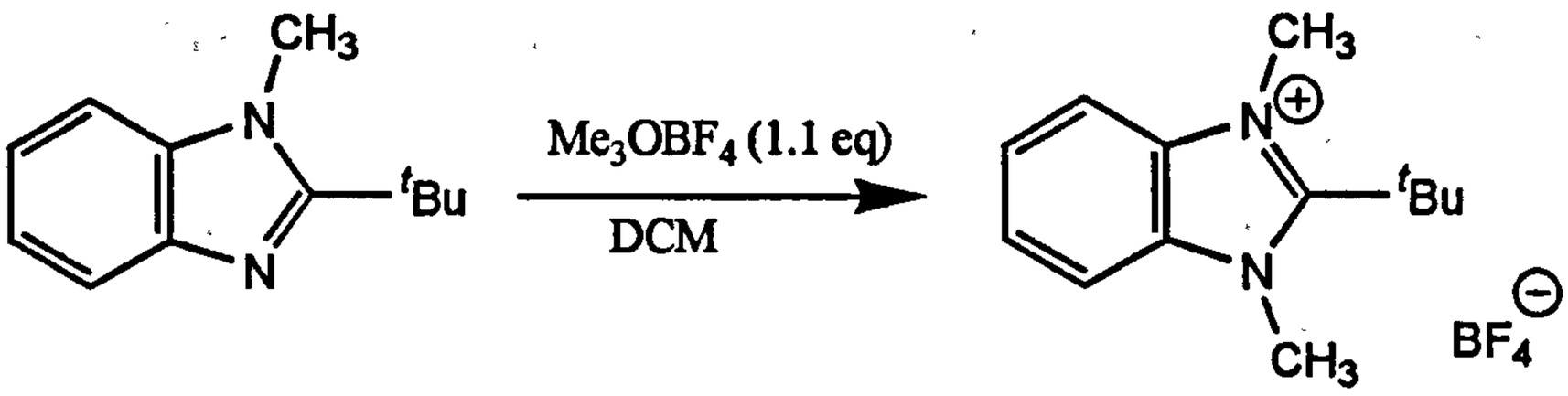
3.3 Synthesis of benzimidazolium salts

3.3.1 1, 3-Dimethyl-2-*t*-butylbenzimidazolium tetrafluoroborate (42)

2-*t*-Butylbenzimidazole was refluxed with methyl iodide in the presence of sodium methoxide for 4 hours in methanol (**Scheme 3.7**). The addition of diethyl ether enabled separation of the products, 1-methyl-2-*t*-butylbenzimidazole (37 %) and 1, 3-dimethyl-2-*t*-butylbenzimidazolium iodide (31 %) by filtration. The imine was treated with Meerwein's reagent in DCM to yield the title compound (**Scheme 3.8**) in 21 % yield overall.



Scheme 3.7

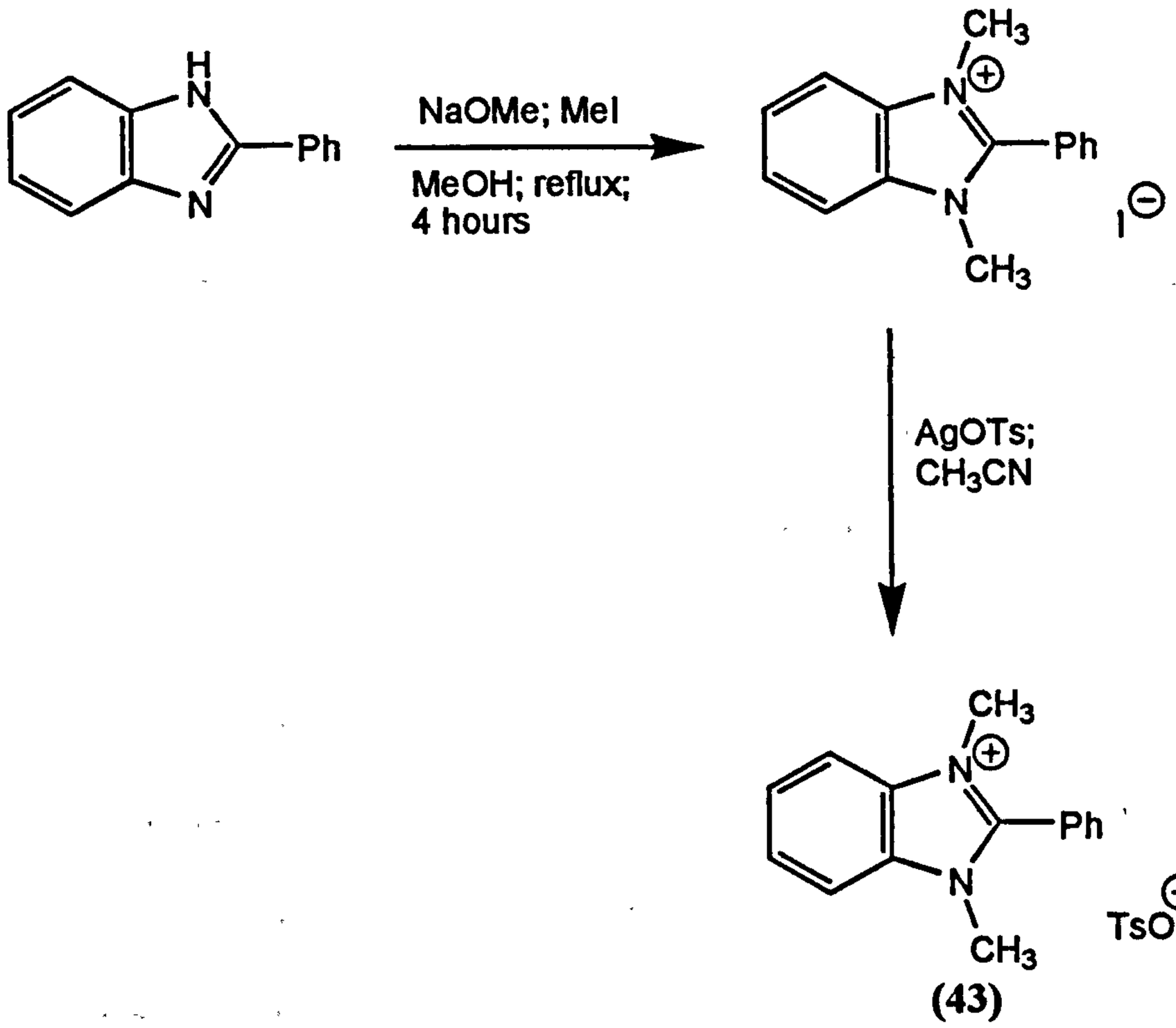


(42)

Scheme 3.8

3.3.2 1, 3-Dimethyl-2-phenylbenzimidazolium tosylate (43)

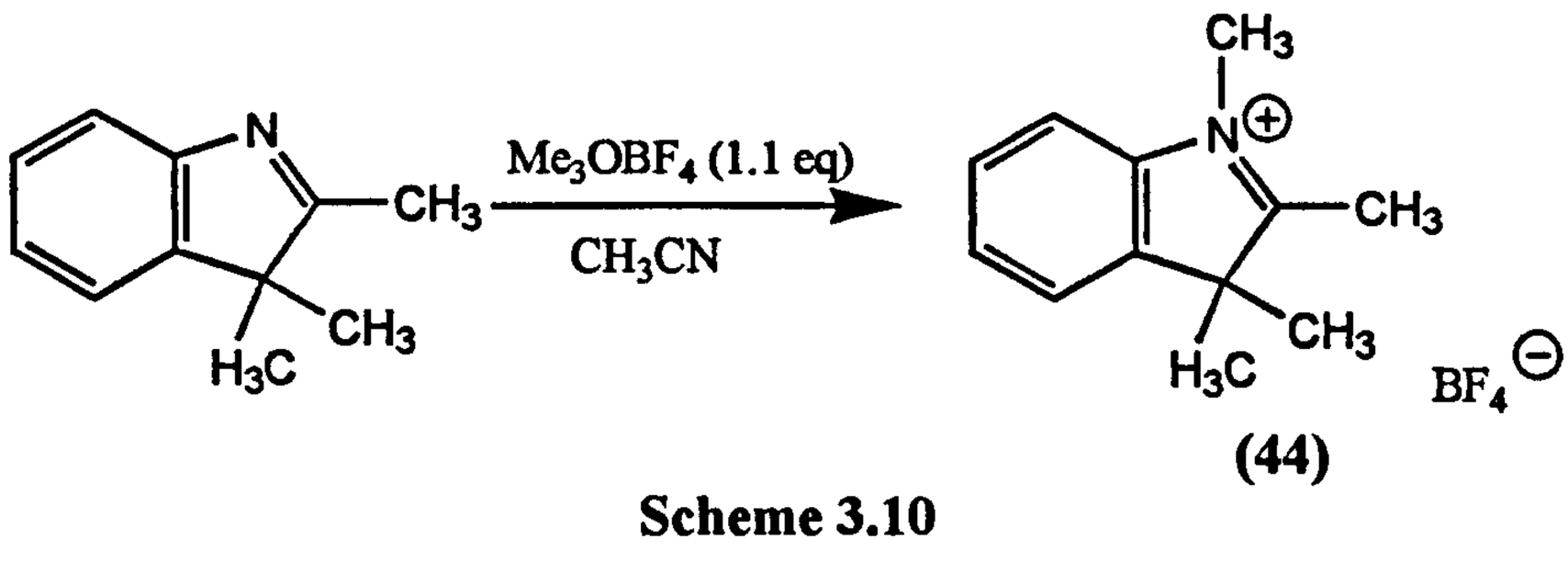
2-Phenylbenzimidazole was refluxed with methyl iodide in the presence of sodium methoxide for 4 hours in methanol. The solution of the iodide salt was added to a solution of silver tosylate in acetonitrile and stirred for 18 hours. The precipitate of silver iodide was removed by filtration and the title compound was recovered from the filtrate (**Scheme 3.9**) in 51 % yield.



Scheme 3.9

3.4 Synthesis of 1,2,3,3-tetramethylindoleninium tetrafluoroborate (44)

1,2,3,3-Tetramethylindoleninium tetrafluoroborate was prepared in a similar manner to the benzoxazolium tetrafluoroborate salts. Reaction of the commercially available 2,3,3-trimethylindolenine with Meerwein's reagent gave a good yield (89 %) of the indoleninium salt after recrystallisation (**Scheme 3.10**).



Scheme 3.10

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Chapter 4

The Use Of Iminium

Salts For The Oxidation Of Thioanisole

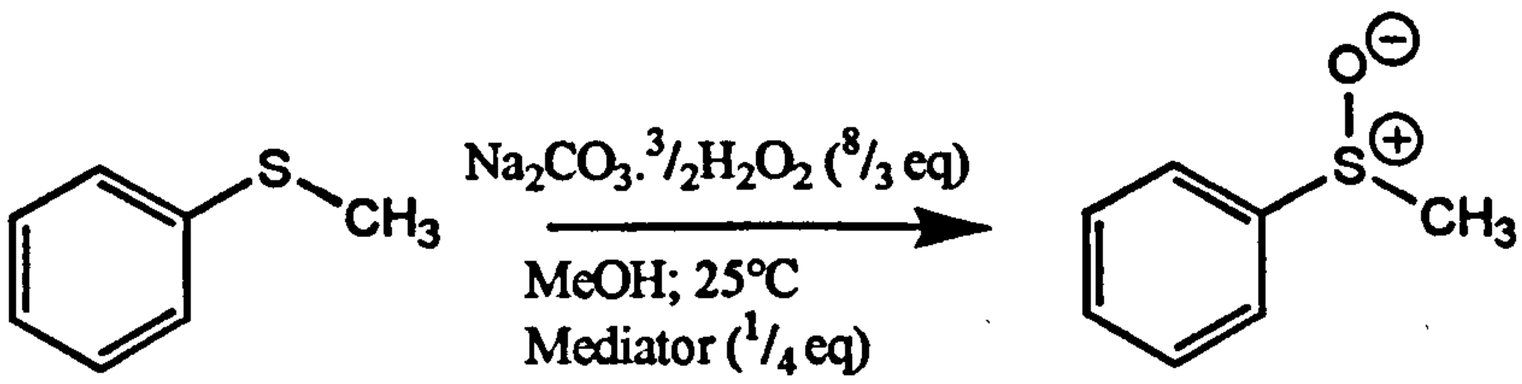
4.1 The use of benzoxazolium mediators for the oxidation of thioanisole

The activity of the benzoxazolium salts was initially tested by monitoring their ability to oxidise sulfides to sulfoxides. This reaction was chosen because it is an electrophilic oxidation and so it is a reasonable model for soil removal in household cleaning. Sodium percarbonate was used as the primary oxidant because this is a source of alkaline hydrogen peroxide. Methanol was employed as the solvent because it is both hydroxylic (like water) and able to dissolve the sulfide. The mediator was used in 25 mole % with respect to the sulfide so that any turnover of the mediator could easily be observed.

Thioanisole (phenyl methyl sulfide) was chosen as the substrate because it is a stable sulfide that is not oxidised too easily. Furthermore, the introduction of substituents into the aromatic ring will allow further investigation into the mediator's reactivity.

The catalysts previously synthesised and the commercially available 2-chloro-3-ethylbenzoxazolium tetrafluoroborate **(41)** were assessed as catalytic mediators for the oxidation of thioanisole under a standard set of conditions (**Scheme 4.1**). Sodium percarbonate was not totally soluble in methanol, making this a two-phase, heterogeneous reaction. Previously, others have shown that sodium percarbonate is able to provide a constant low concentration of hydrogen peroxide if the bulk of the solid is undissolved in the organic solvent.[1] The concentration of hydrogen peroxide in solution was confirmed to be the same at the beginning and the end of the reactions by titration against standard sodium thiosulfate solution. The reactions, which contain undissolved sodium percarbonate, will be referred to as 'heterogeneous reactions' throughout the remainder of the thesis.

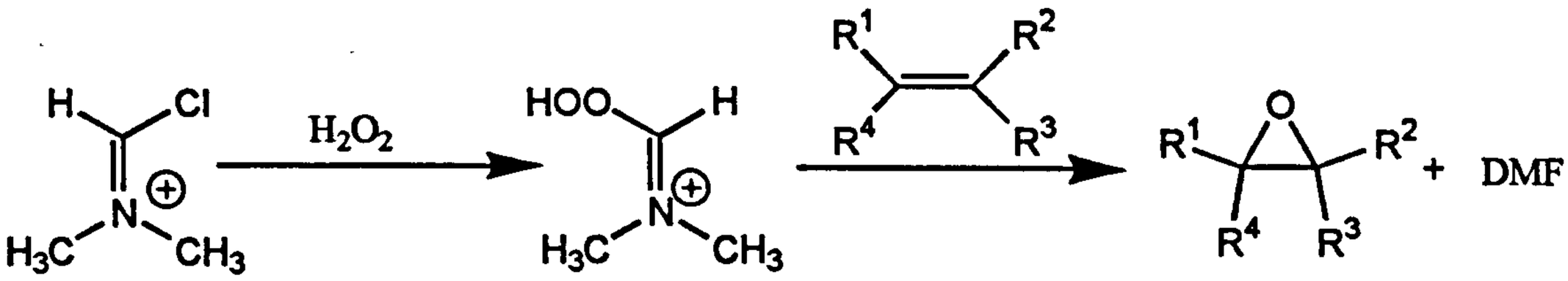
The oxidation of thioanisole was also carried out in the absence of any mediator in order to measure the amount of direct oxidation by sodium percarbonate. After 24 hours there was less than 5 % conversion of sulfide ($[S]_0 = 0.28$ mol.L^{-1}) in the uncatalysed reaction.



Scheme 4.1 General reaction scheme for the oxidation of thioanisole

The mediator (25 mole % with respect to the sulfide) was added to a solution of thioanisole in methanol with sodium percarbonate as the oxidant (present in an amount that corresponds to four equivalents of hydrogen peroxide). The reaction temperature was maintained at 25°C by the use of a thermostatted waterbath. Aliquots were taken at appropriate time intervals and analysed by reversed-phase HPLC (using biphenyl as an internal standard). The amount of phenyl methyl sulfoxide formed after 24 and 48 hours is shown for each benzoxazolium salt in **Table 4.1** (the amounts shown also agree well with sulfide consumption). ^{1}H NMR and mass spectra of the crude reaction mixtures were also run in order to aid identification of the components of the mixtures.

The 2-chloro-substituted salt **(41)** was expected to be particularly interesting since it resembled the Vilsmeier reagent **(45)**,[2] which has been used in conjunction with hydrogen peroxide for the epoxidation of various olefins (**Scheme 4.2**); in such reactions 1.2-3.6 equivalents (with respect to olefin) were used.[3]



(45) **(46)**

Scheme 4.2

Table 4.1 The oxidation of thioanisole by 2-substituted benzoxazolium salts

Entry	R	Y	Compound	% Conversion (24 hours)	% Conversion (48 hours)
1	H	BF_4	**(35)**	33	40
2	CH_3	TsO	**(47)**	29	34
3	Cl	BF_4	**(41)**	66	n.d.
4	Ph	BF_4	**(36)**	32	37
5	*t*-Bu	BF_4	**(37)**	29	31

% Conversion = no. of moles sulfoxide/ (no. of moles sulfoxide + no. of moles sulfide)

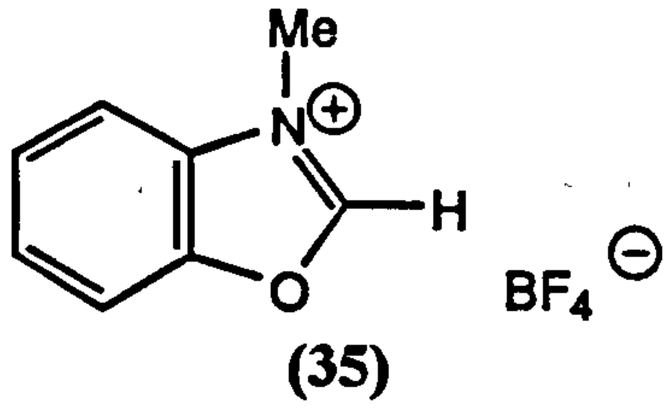
During all of the reactions, the reaction mixture became coloured after the addition of the mediator. In all cases no mediator could be detected by TLC upon completion of the reaction. The amount of hydrogen peroxide remaining in solution

was calculated by titration of liberated iodine against standard sodium thiosulfate solution.

The reactions of 2-alkyl or 2-aryl benzoxazolium salts appear to yield a stoichiometric amount of phenyl methyl sulfoxide i.e. one mole of sulfoxide is formed per mole of mediator added **(Table 4.1)**. This suggests that the reaction is not catalytic and the mediator is not reformed in a catalytic cycle. The reactions begin quickly, but then the rate starts to tail off rather sharply **(Figure 4.1)**. After 360 mins (21600 s) the rate becomes the same for both mediators (approximately 4 times the rate of the uncatalysed reaction).

2-Chloro-3-ethylbenzoxazolium tetrafluoroborate **(41)** gave more than twice as much sulfoxide as the amount of mediator initially added (entry 3). The rate of sulfoxide production was faster than for the 2-alkyl or 2-aryl benzoxazolium salts **(29)**. The rate of reaction is rapid for the first 14400 s and then the rate slows down rapidly. No sulfone formation was observed in any of the cases.

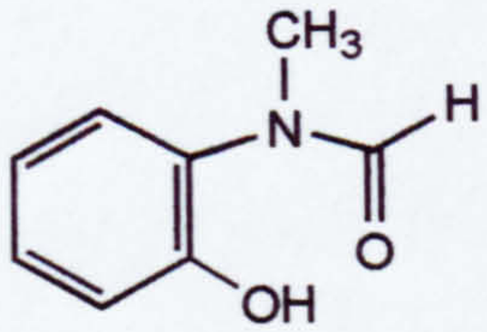
4.1.1 3-Methylbenzoxazolium tetrafluoroborate (35) as a mediator



(35)

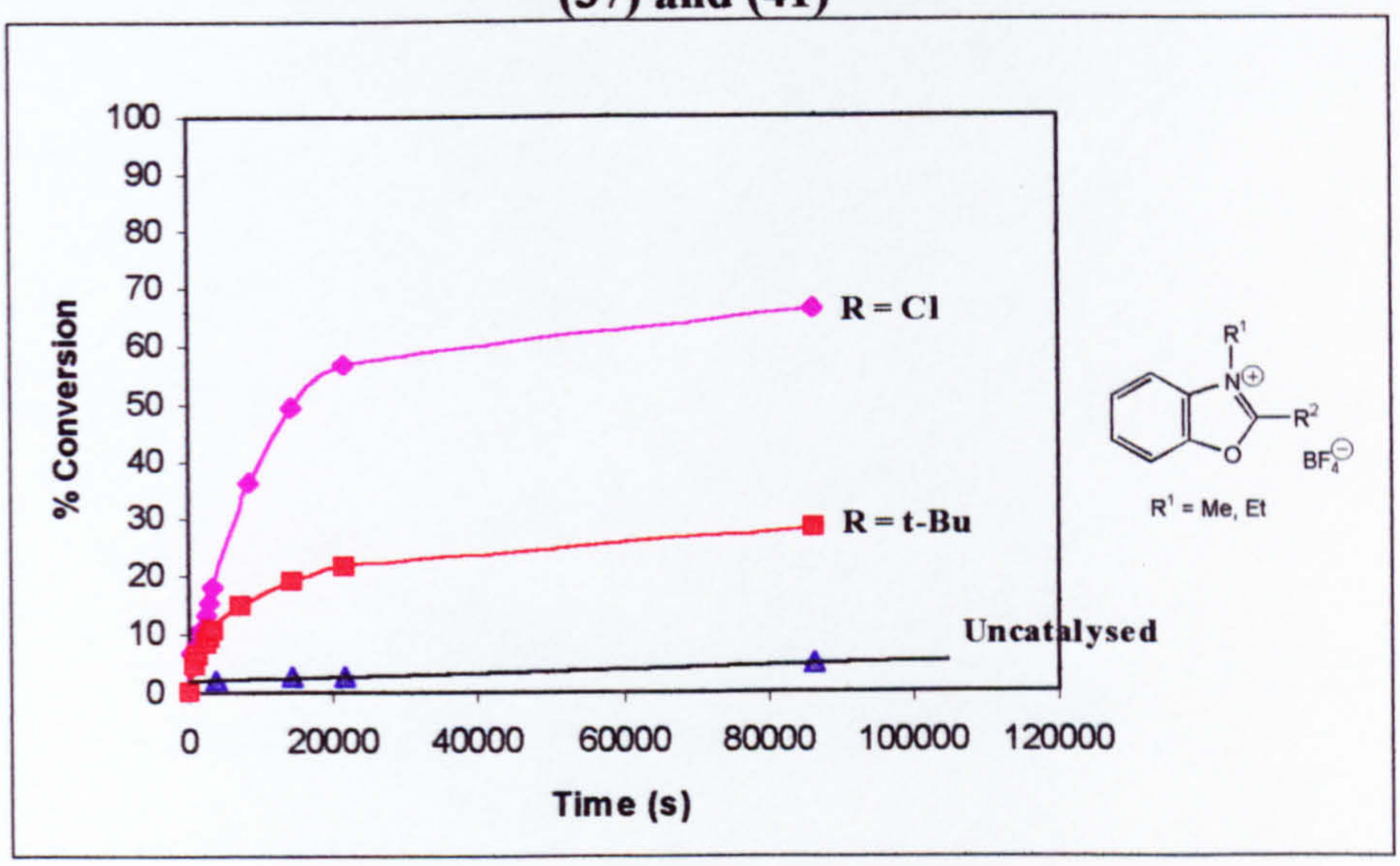
The ^{1}H NMR spectrum of the crude reaction mixture from thioanisole oxidation revealed, besides singlets at 2.4 ppm (CH_3-S) and 2.7 ppm (CH_3-SO) corresponding to methyl groups in the sulfide and sulfoxide respectively, two new resonances: a singlet at 3.2 ppm and a singlet at 8.2 ppm. There were no signals corresponding to the mediator at 4.4 ppm (N-CH_3) or 10.3 ppm (N=C-H). In the mass spectrum of the crude reaction mixture there was a peak at m/z = 151.

An authentic sample of *N*-(2-hydroxyphenyl)-*N*-methyl-formamide **(48)** was prepared by hydrolysis of **(35)**. By comparison of the ^{1}H NMR spectrum, the mass spectrum and the HPLC chromatogram to the data obtained for the crude reaction mixture, the presence of **(48)** in the mixture was confirmed.

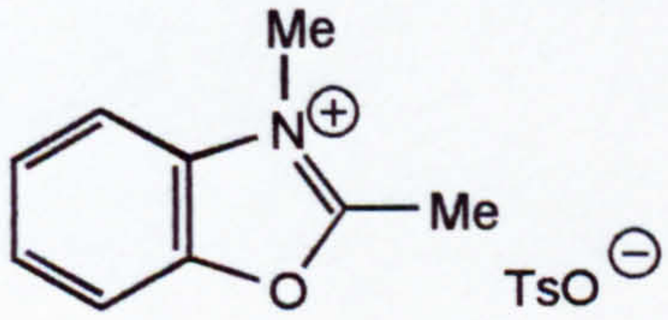


(48)

Figure 4.1 Graph To Show Production Of Sulfoxide At 25°C By Compounds (37) and (41)



4.1.2 2,3-Dimethylbenzoxazolium tosylate (47) as a mediator

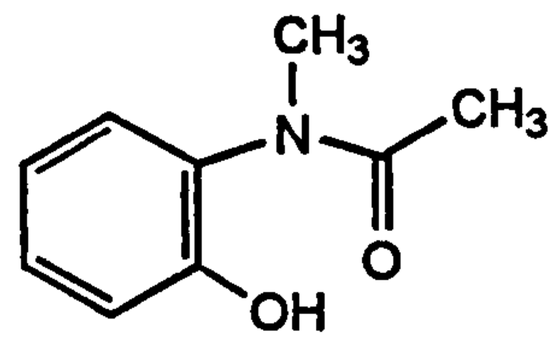


(47)

In addition to singlets at 2.4 ppm and 2.7 ppm, corresponding to *S*-methyl groups in the sulfide and sulfoxide respectively, the ^{1}H NMR spectrum of the crude reaction mixture from oxidation of thioanisole by **(47)** showed two new resonances: a singlet at 1.9 ppm and a singlet at 3.2 ppm. There were no signals corresponding to the mediator (singlets at 3.2 ppm (N=C-CH_3) and 4.3 ppm (N-CH_3)). There was a peak at m/z = 165 in the mass spectrum of the crude reaction mixture.

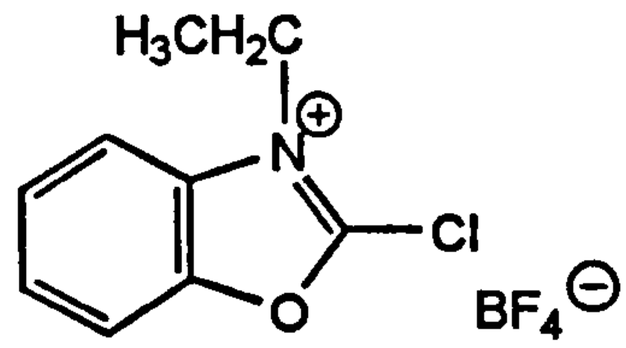
An authentic sample of *N*-(2-hydroxyphenyl)-*N*-methyl-acetamide **(49)** was prepared (by hydrolysis of **(47)**) and its ^{1}H NMR, mass spectral and HPLC data were compared to that for the crude reaction mixture. This confirmed that **(49)** was present

in the reaction mixture. Others have shown previously that **(49)** is formed from the hydrolysis of 2,3-dimethylbenzoxazolium tosylate **(47)**.[4]



(49)

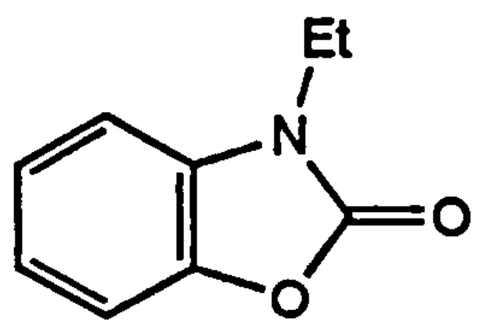
4.1.3 2-Chloro-3-ethylbenzoxazolium tetrafluoroborate (41) as a mediator



(41)

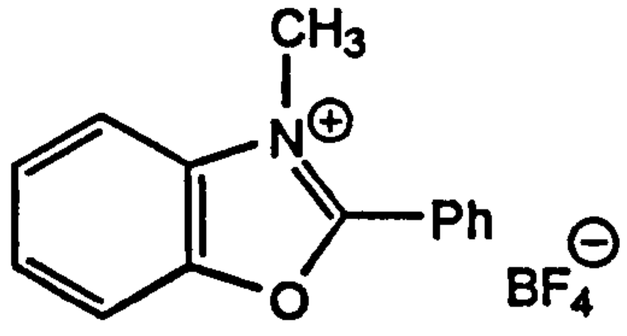
There were no signals (triplet at 1.3 ppm and quartet at 3.9 ppm) corresponding to the benzoxazolium salt in the ^{1}H NMR spectrum of the crude reaction mixture from the oxidation of thioanisole. There were peaks corresponding to the *S*-methyl groups of the sulfide and sulfoxide at 2.4 ppm and 2.7 ppm respectively, as well as two new resonances: a triplet at 1.3 ppm and a quartet at 3.8 ppm. The mass spectrum of the reaction mixture displayed a peak at m/z = 163.

This spectral data, along with the HPLC chromatogram, was compared to data from an authentic sample of 3-ethylbenzoxazolinone **(50)** (prepared by dissolving **(41)** in deuterium oxide and extraction into DCM) and indicated that it was present in the reaction mixture.



(50)

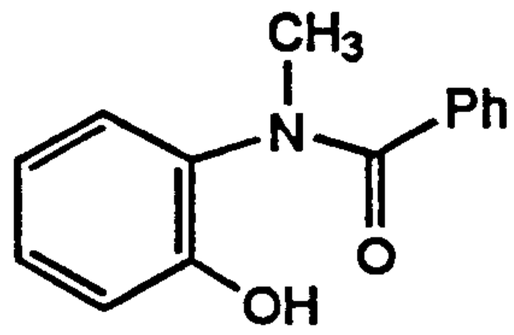
4.1.4 2-Phenyl-3-methylbenzoxazolium tetrafluoroborate (36) as a mediator



(36)

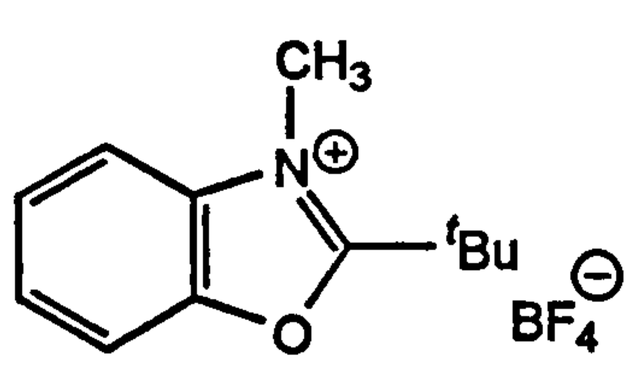
The ^{1}H NMR spectrum of the crude thioanisole oxidation mixture revealed a new singlet at 3.2 ppm, as well as peaks corresponding to the sulfide and sulfoxide at 2.4 ppm (CH_3-S) and 2.7 ppm (CH_3-SO). There were no signals corresponding to the mediator (i.e. a resonance at 4.6 ppm). In the mass spectrum of the reaction mixture there was a peak at m/z = 227.

An authentic sample of *N*-(2-hydroxy-phenyl)-*N*-methylbenzamide **(51)** was prepared. When the mass spectral, ^{1}H NMR and HPLC data were compared to the data obtained for the reaction mixture, the presence of **(51)** was confirmed. This compound was also reported to be formed from the hydrolysis of 2-phenyl-3-methylbenzoxazolium tosylate by Ott in 1956.[5]



(51)

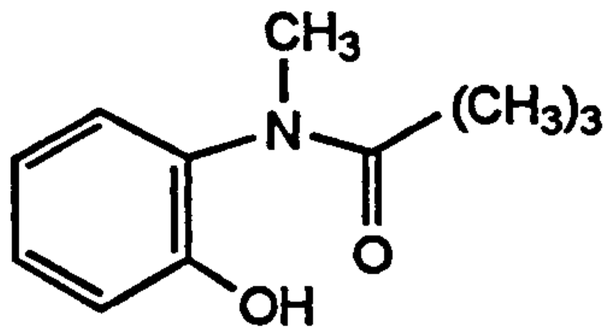
4.1.5 2-*tert*-Butyl-3-methylbenzoxazolium tetrafluoroborate (37) as a mediator



(37)

Besides peaks corresponding to the sulfide and sulfoxide at 2.4 ppm (CH_3-S) and 2.7 ppm (CH_3-SO), the ^{1}H NMR spectrum of the crude oxidation mixture showed two new singlets at 1.0 ppm and 3.1 ppm. No signals corresponding to the mediator were present (1.8 and 4.3 ppm). There was a peak at m/z = 207 in the mass spectrum of the crude reaction mixture.

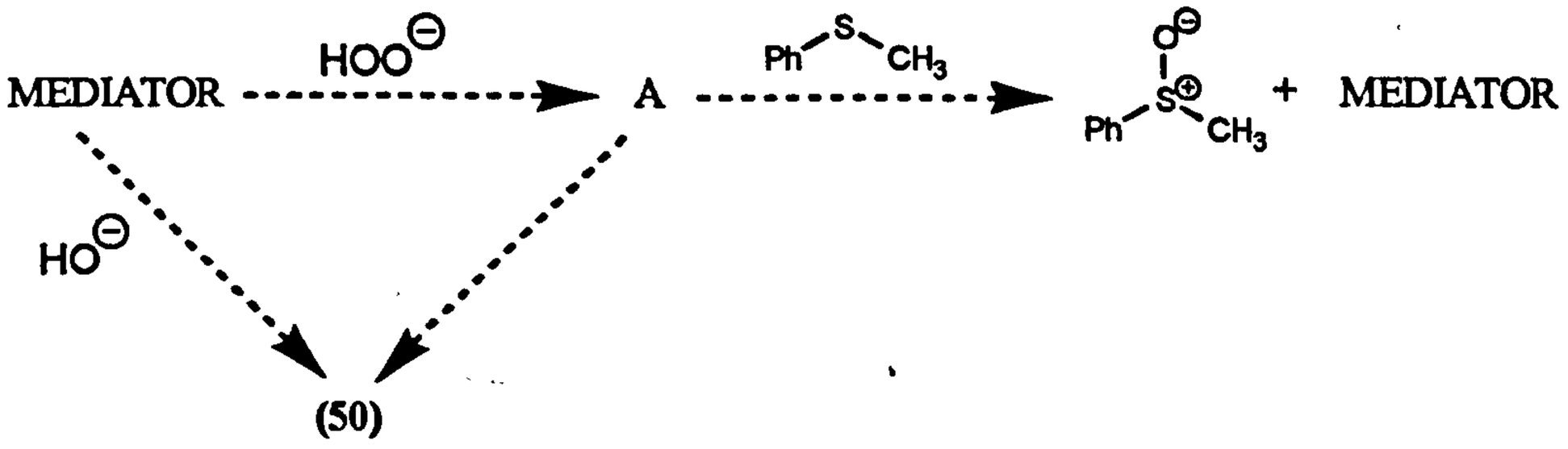
An authentic sample of *N*-(2-hydroxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide **(52)** was prepared by the basic hydrolysis of **(37)**. By comparing the mass spectral, ^{1}H NMR and chromatographic data, it was confirmed that *N*-(2-hydroxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide **(52)** was formed from the mediator during the oxidation.



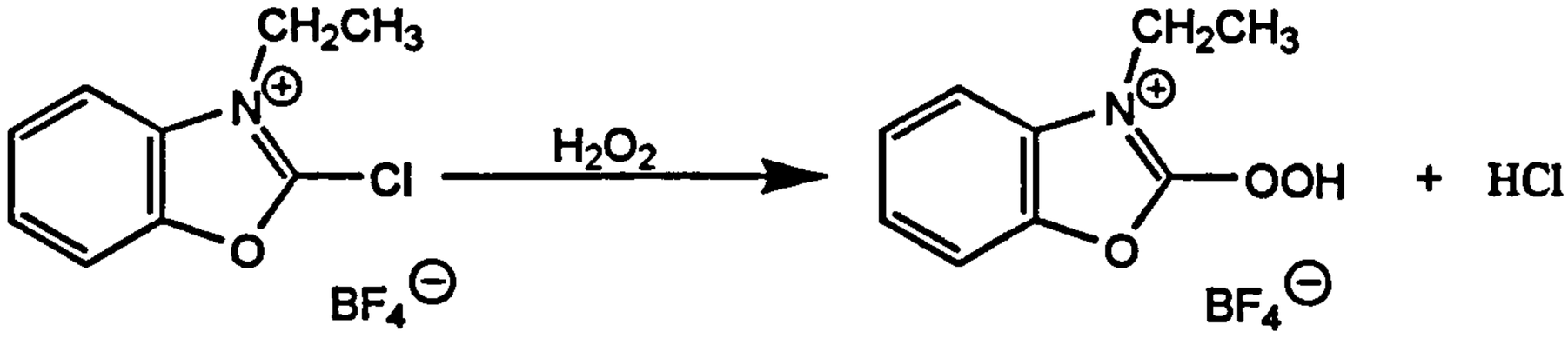
(52)

4.1.6 Discussion

2-Chloro-3-ethylbenzoxazolium tetrafluoroborate was converted under the reaction conditions into 3-ethylbenzoxazolinone **(50)**. The fact that more than two moles of sulfoxide are formed per mole of benzoxazolium salt means that there is turnover and catalysis in this case. Thus, the mediator must react with hydrogen peroxide to form an active oxidant, which then oxidises the sulfide and reforms the iminium salt or another compound that can activate hydrogen peroxide. The formation of compound **(50)** can be explained by the gradual depletion of the mediator or a compound formed from it in a separate process **(Scheme 4.3)** (the dashed arrows are used to indicate that the processes may not take place in one step). In epoxidations performed using the Vilsmeier reagent **(45)** and hydrogen peroxide, the authors suggest that the active oxidant is a hydroperoxy iminium salt **(46)**, **(Scheme 4.2)**; a similar compound could be formed from **(41)** and hydrogen peroxide.



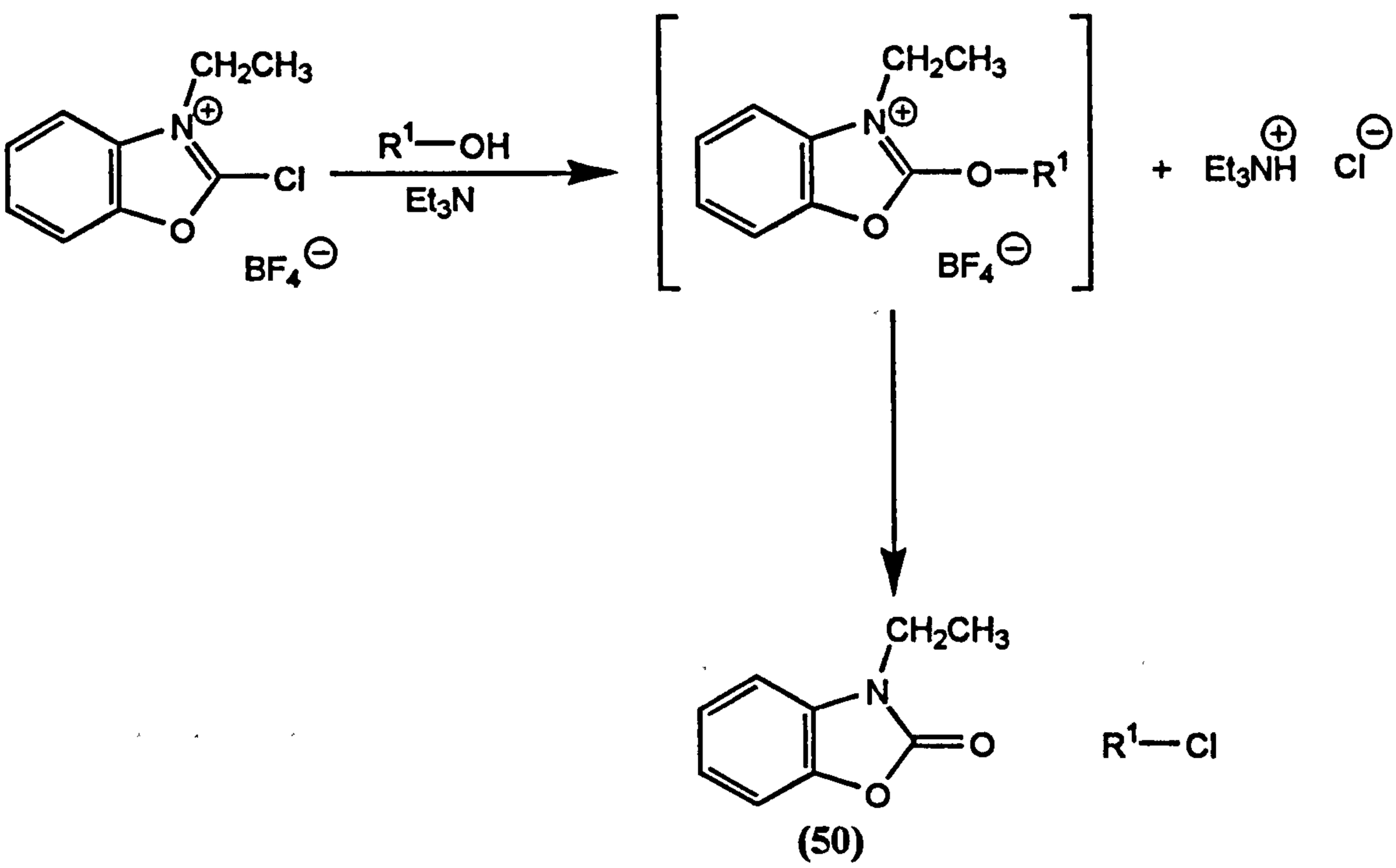
Scheme 4.3



Scheme 4.4

2-Chloro-3-ethylbenzoxazolium tetrafluoroborate has been reported to react with alcohols in the presence of base to yield the corresponding alkyl chlorides and compound **(50)** **(Scheme 4.5)**.[6] Thus, one possibility is that compound **(50)** is formed

in this fashion, although in the oxidations, the possible presence of chloromethane was not examined.

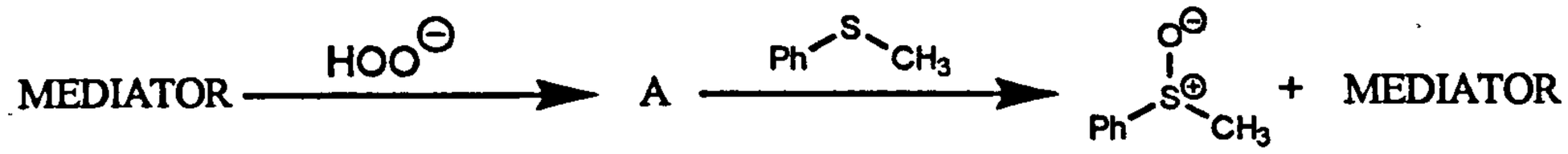


(50)

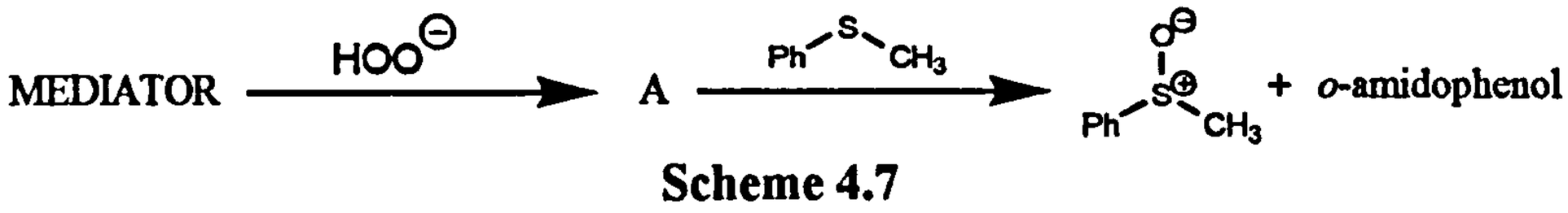
Scheme 4.5

Electron deficient carbonyl compounds have themselves been used in conjunction with hydrogen peroxide for oxygen transfer,[7, 8] so it is conceivable that 3-ethylbenzoxazolinone **(50)** could mediate the reaction in a catalytic manner. The ability of 3-ethylbenzoxazolinone **(50)** to oxidise thioanisole under the standard reaction conditions was investigated. It was discovered that the oxidation did not proceed any further than the uncatalysed reaction. Thus 3-ethylbenzoxazolinone **(50)** does not react with hydrogen peroxide to form a species capable of oxidising thioanisole.

Investigation of the fate of the 2-alkyl and 2-arylbenzoxazolium salts has revealed that the mediators are converted into the corresponding *o*-amidophenols. Two possible pathways for the conversion of the benzoxazolium salts into *o*-amidophenols under the reaction conditions are envisaged. One possibility is that the oxidation of the sulfide is catalytic (i.e. the iminium salt is reformed) and the hydrolysis of the iminium salt takes place in an unrelated process (**Scheme 4.6**); alternatively the oxidation is stoichiometric and the mediator is converted to an *o*-amidophenol in the process of *O*-transfer (**Scheme 4.7**).



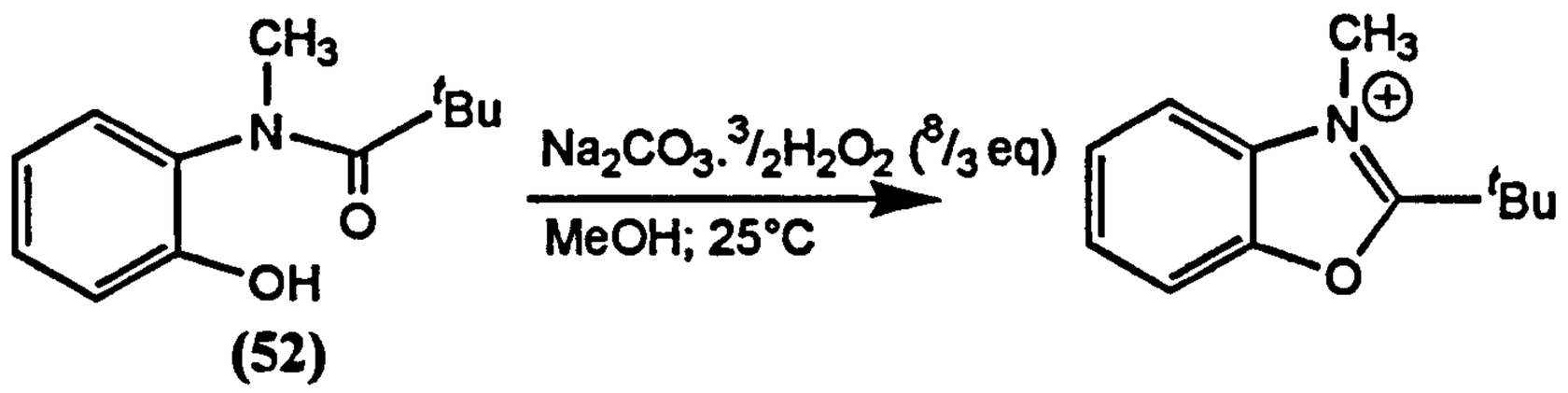
Scheme 4.6



Scheme 4.7

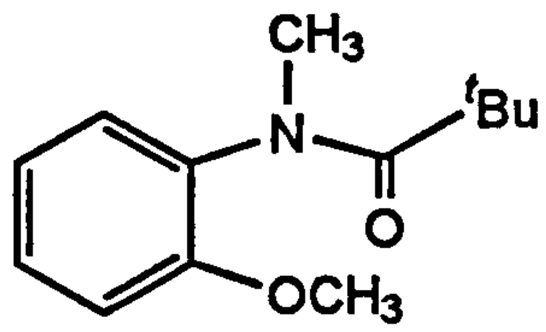
The amount of phenyl methyl sulfoxide formed in each case appears to correspond approximately to the amount of mediator added (25 % conversion) plus a small amount formed from the uncatalysed reaction (5 % conversion). This seems to favour the pathway shown in (**Scheme 4.7**), although one can still not rule out the possibility that the oxidation is catalytic (however, see **Section 4.4**).

To determine whether the *o*-amidophenol formed from the benzoxazolium salts is able to activate hydrogen peroxide towards the oxidation of thioanisole, *N*-(2-hydroxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide **(52)** and *N*-(2- methoxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide **(53)** were synthesised and used as mediators under the standard reaction conditions. Under the conditions of the reaction it may be possible for compound **(52)** to reform the benzoxazolium ring and thus mediate the reaction (**Scheme 4.8**). Compound **(53)** however is unable to reform the benzoxazolium ring.



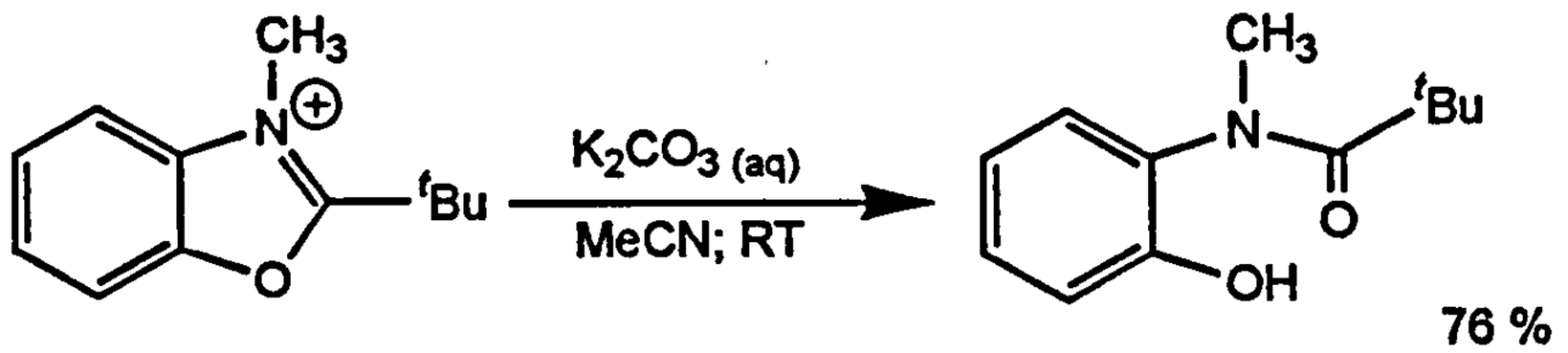
(52)

Scheme 4.8



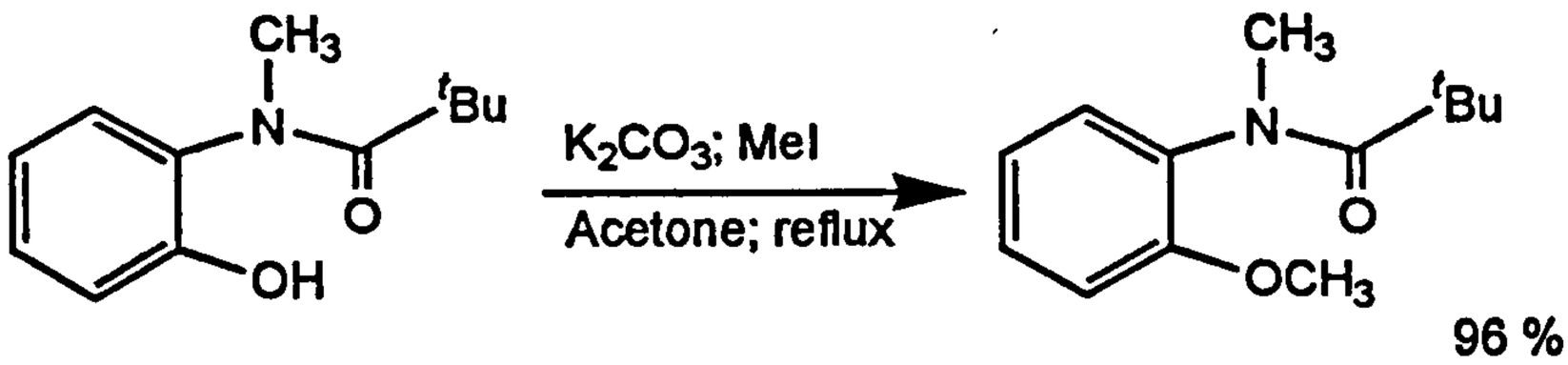
(53)

N-(2-Hydroxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide **(52)** was synthesised by the hydrolysis of 2-*t*-butyl-3-methylbenzoxazolium tetrafluoroborate by aqueous potassium carbonate solution **(Scheme 4.9)**.



Scheme 4.9

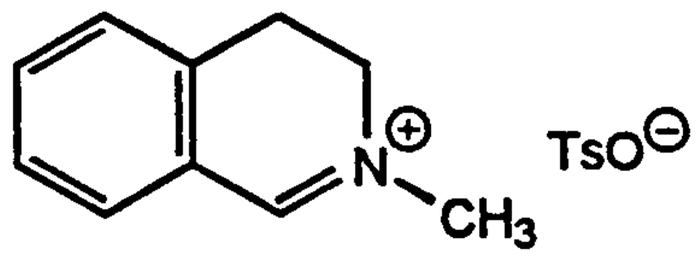
N-(2-Hydroxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide **(52)** was refluxed in acetone with methyl iodide and potassium carbonate to yield *N*-(2-methoxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide **(53)**.



Scheme 4.10

Compound **(52)** produced phenyl methyl sulfoxide in 23 % yield after 24 hours, which is almost as much as that produced by 2-*t*-butyl-3-methylbenzoxazolium tetrafluoroborate (29 %) under the same conditions. However **(53)** only gave 7 % sulfoxide, which is little enhancement over the uncatalysed reaction. These two results show that **(52)** is able to activate hydrogen peroxide towards the oxidation of thioanisole. One possibility is that the benzoxazolium salt can be reformed, although the manner in which this might occur is unclear. When *N*-(2-hydroxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide **(52)** was treated with sodium percarbonate in d^4 methanol **(Scheme 4.9)**, there was no evidence of benzoxazolium salt formation (i.e. singlets at 1.8 ($N=C-C(CH_3)_3$) and 4.3 ppm ($N-CH_3$)) in the ^1H NMR spectrum.

4.1.7 *N*-Methyl-3, 4-dihydroisoquinolinium tosylate (54) as a mediator



(54)

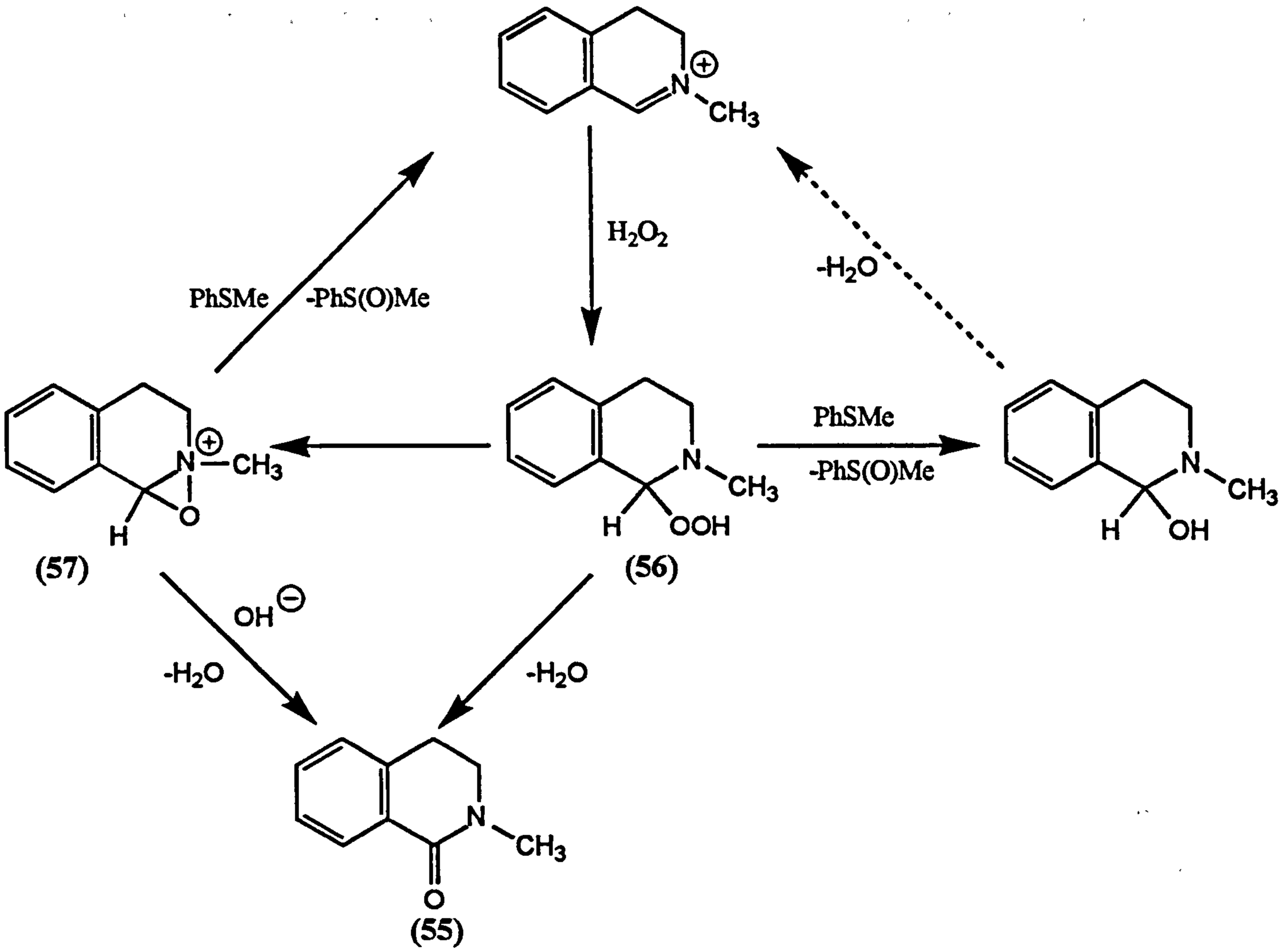
Since the benzoxazolium salts were much poorer at mediating the transfer of oxygen from hydrogen peroxide to sulfides than expected, the standard oxidation reaction was carried out using *N*-methyl-3, 4-dihydroisoquinolinium tosylate **(54)** as the mediator.

Unilever Research Ltd. has used this compound with some success for soil removal in hard-surface cleaning. It is used as a benchmark in standard tests of new organic activators of hydrogen peroxide. Furthermore, this iminium salt is known to be active for the transfer of oxygen from Oxone® or peracids to olefins.[9, 10]

Surprisingly, this iminum salt also appeared to generate a stoichiometric amount of sulfoxide under these conditions (23 %). The reaction did not proceed any further than expected from the uncatalysed reaction over the next 24 hours (27 %).

The lactam **(55)** was detected in the HPLC chromatogram (it had the same retention time as the authentic compound). The ^{1}H NMR spectrum of the crude reaction mixture also showed resonances (triplets at 2.9 and 3.5ppm (CH_2-CH_2); singlet at 3.1 ppm (N-CH_3)) corresponding to the presence of the lactam. A peak was observed at m/z = 161 in the mass spectrum, as would be expected if the lactam was present in the reaction mixture.

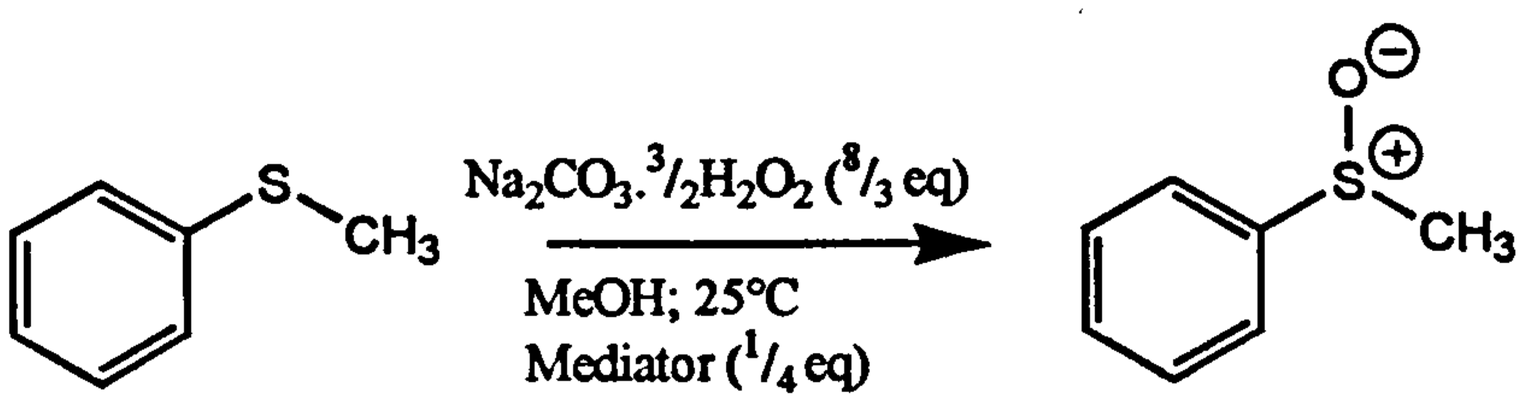
There are two possible routes that this reaction can follow. The initial reaction of the iminium salt with hydrogen peroxide initially gives a hydroperoxyamine **(56)**, which could be the active oxidant; alternatively, this compound could firstly be transformed into an oxaziridinium salt **(57)** which then oxidises the sulfide and reforms the iminium salt. The lactam could be formed by deprotonation of the oxaziridinium salt or alternatively by dehydration of the hydroperoxyamine (**Scheme 4.11**). Other authors have suggested that the intermediate is the oxaziridinium salt since this compound has been isolated from reaction of the iminium salt with Oxone or mCPBA.[11] However, this does not prove that the oxaziridinium salt is formed as an intermediate when the primary oxidant is hydrogen peroxide.



Scheme 4.11

4.2 The use of benzothiazolium mediators for the oxidation of thioanisole

The benzothiazolium salts previously synthesised were assessed as catalytic mediators for the oxidation of thioanisole under the standard set of reaction conditions (**Scheme 4.1**).



Scheme 4.1 General reaction scheme for the oxidation of thioanisole

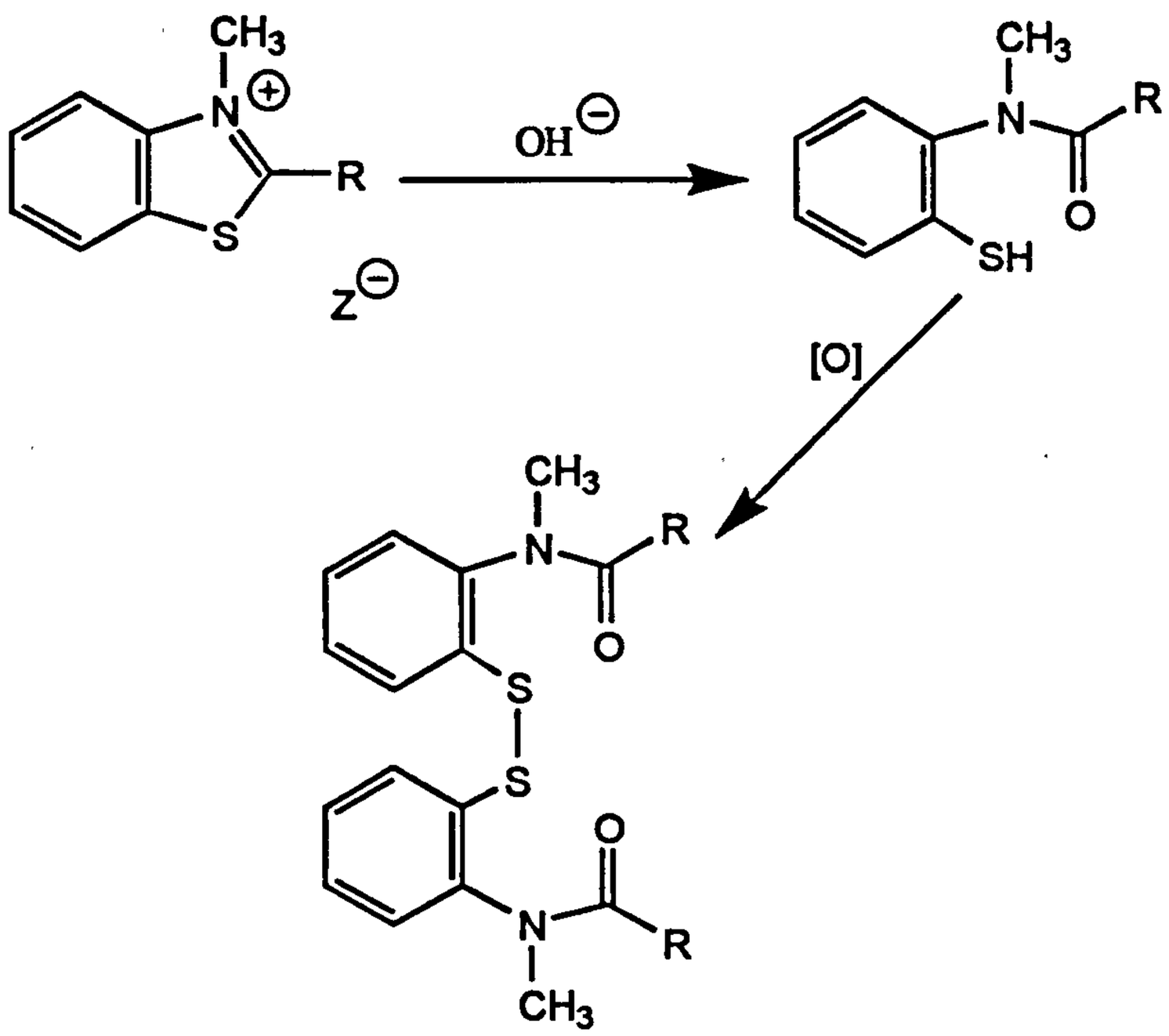
Aliquots were taken at appropriate time intervals and analysed by reversed-phase HPLC (using biphenyl as an internal standard). The amount of phenyl methyl sulfoxide formed after 24 and 48 hours is shown for each benzothiazolium salt in **Table 4.2**. ^{1}H NMR and mass spectra of the crude reaction mixtures were also taken.

Table 4.2 The oxidation of thioanisole by 2-substituted benzothiazolium salts

Entry	R	Y	Compound	% Conversion (24 hours)	% Conversion (48 hours)
1	H	BF_4	(38)	23	28
2	CH_3	TsO	(58)	16	n.d.
3	Ph	BF_4	(39)	11	15
4	*t*-Bu	BF_4	(40)	12	16

% Conversion = no. of moles sulfoxide/ (no. of moles sulfoxide + no. of moles sulfide)

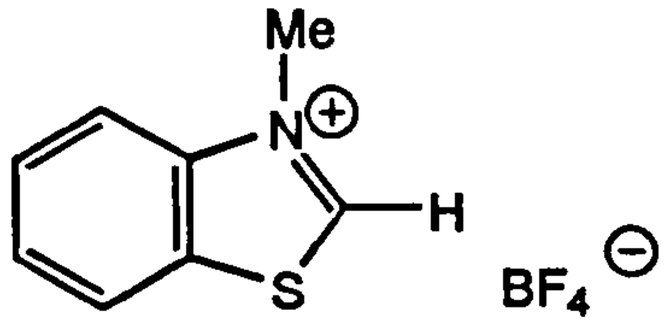
The 2-alkyl benzothiazolium salts gave much less phenyl methyl sulfoxide than the corresponding 2-alkyl benzoxazolium salts, with the unsubstituted (entry 1) and 2-methyl compounds (entry 2) being the most effective. Since there is less than a stoichiometric amount (with respect to mediator) of sulfoxide formed in the oxidations, it is likely that the benzothiazolium salts are also consumed in a process separate from the oxidation. Benzothiazolium salts have been shown to undergo hydrolysis in a similar manner to the corresponding benzoxazolium salts, except that under the oxidative conditions of the reaction they form disulfides after ring opening (**Scheme 4.12**).[12] The same compounds were also reported by Ohsawa who synthesised them from the oxidation of benzothiazolium salts with potassium superoxide.[13]



Scheme 4.12

During all of the reactions, the reaction mixture became coloured after the addition of the mediator. Upon completion of the reaction no mediator could be detected by TLC in all cases. The amount of hydrogen peroxide remaining in solution was calculated by titration of liberated iodine against standard sodium thiosulfate solution.

4.2.1 3-Methylbenzothiazolium tetrafluoroborate (38) as a mediator

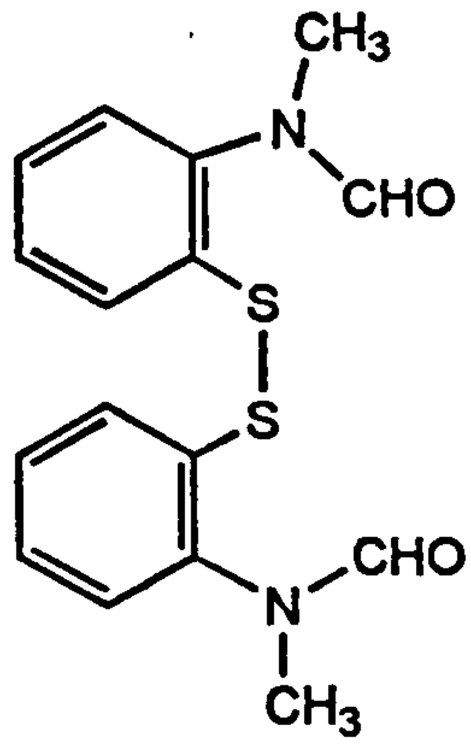


(38)

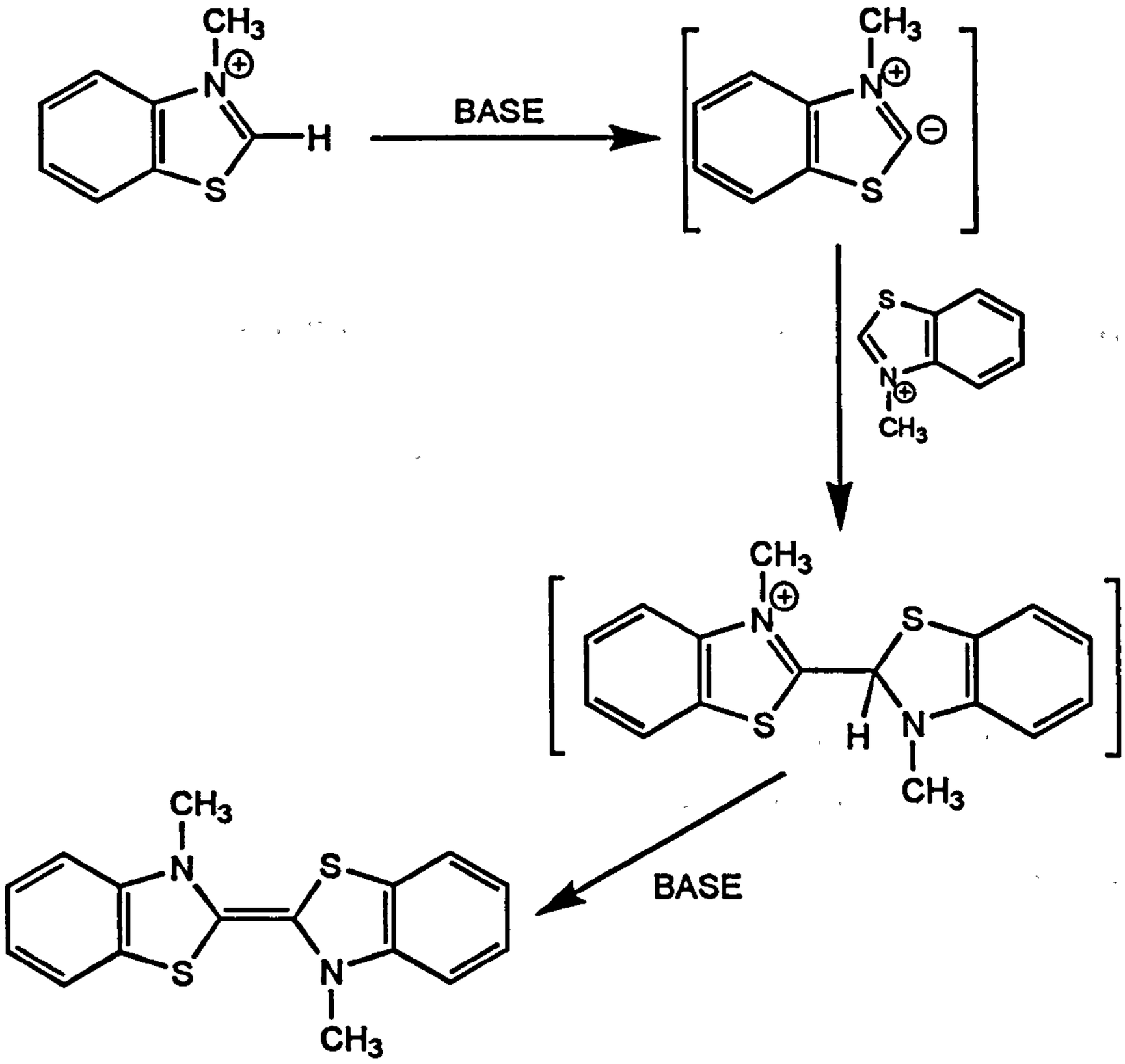
A ^{1}H NMR spectrum of the crude thioanisole oxidation mixture revealed, besides peaks corresponding to the *S*-methyl groups of the sulfide and sulfoxide at 2.4 and 2.7 ppm, four new resonances: singlets at 3.17 ppm, 3.34 ppm, 8.01 ppm and 8.15 ppm. There were no signals corresponding to the mediator. These values are in agreement with the published literature values for the conformational isomers of *bis*-(2-(*N*-formyl-*N*-methylamino)phenyl)disulfide **(59)**.[13] Under the reaction conditions the ratio of isomers was 3:1 (calculated from integration of the ^{1}H NMR spectrum). There were no peaks at 4.3 ppm or 10.1 ppm as would be expected if the mediator was present in the reaction mixture. The mass spectrum of the crude reaction mixture revealed a peak at m/z = 332, which also indicates the presence of **(59)** in the reaction mixture.

3-Methylbenzothiazolium methylsulfate has also been reported to form 3, 3'-dimethyl-3*H*, 3'*H*-(2, 2')bibenzothiazolylidene (as a mixture of isomers)[14] in basic solution **(Scheme 4.13)**, but this compound was not observed in the reactions.

A separate experiment, using identical reaction conditions but in the absence of sulfide was carried out. The ^{1}H NMR and mass spectra confirmed that the mediator is transformed into the disulfide **(59)**, which was first observed by Clark in 1923.[12]

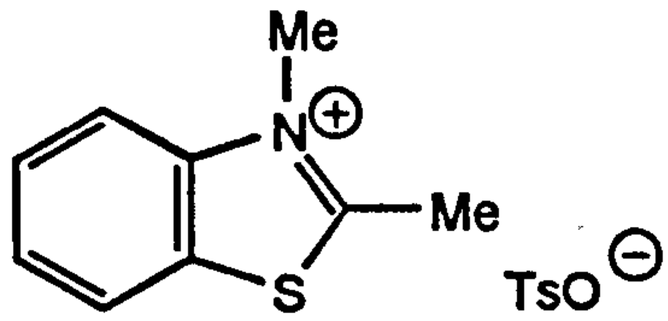


(59)



Scheme 4.13

4.2.2 2,3-Dimethylbenzothiazolium tosylate (58) as a mediator

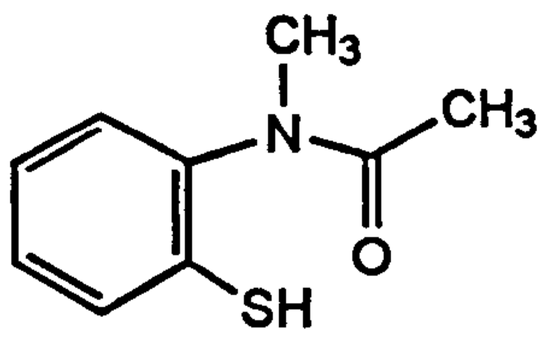


(58)

A ^{1}H NMR spectrum of the crude reaction mixture from thioanisole oxidation showed two singlets: one at 1.9 ppm and one at 3.2 ppm, as well as peaks

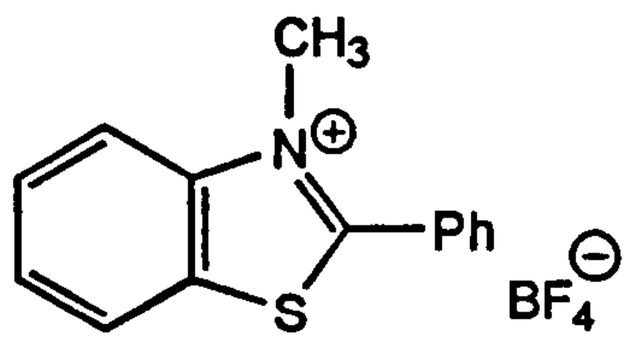
corresponding to the sulfide and sulfoxide at 2.4 and 2.7 ppm respectively. There were no signals corresponding to the mediator, which would be seen at 3.1 and 4.1 ppm. There was a peak at m/z = 181 in the mass spectrum.

N-(2-Mercaptophenyl)-*N*-methyl-acetamide was prepared by the hydrolysis of **(58)** in sodium carbonate solution. Its mass and ^{1}H NMR spectra were compared to those obtained for the crude reaction mixture and both support the conclusion that **(60)** is formed from the mediator under the reaction conditions. This compound was also detected in the HPLC chromatogram of the crude reaction mixture.



(60)

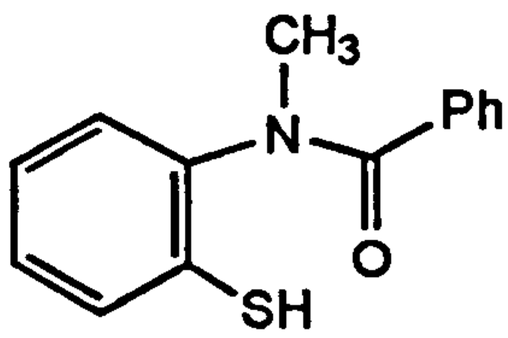
4.2.3 2-Phenyl-3-methylbenzothiazolium tetrafluoroborate (39) as a mediator



(39)

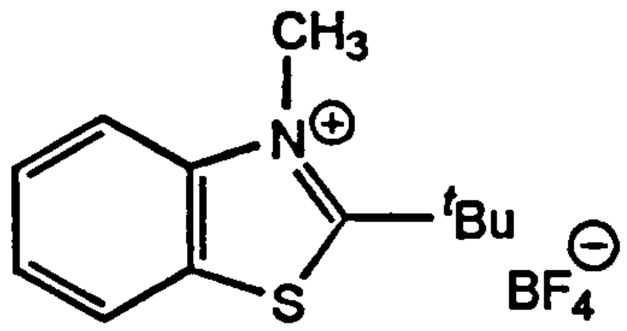
A new singlet at 3.4 ppm was revealed in the ^{1}H NMR spectrum of the crude oxidation mixture. There were signals corresponding to the *S*-methyl groups of the sulfide (2.4 ppm) and sulfoxide (2.7 ppm), but none corresponding to the mediator (4.5 ppm). In the mass spectrum of the reaction mixture there was a peak at m/z = 243.

This data, along with the HPLC chromatogram, was compared to data from an authentic sample (prepared by hydrolysis of **(39)**). This validated the conclusion that *N*-(2-mercapto-phenyl)-*N*-methylbenzamide **(61)** is formed from the mediator under the reaction conditions.



(61)

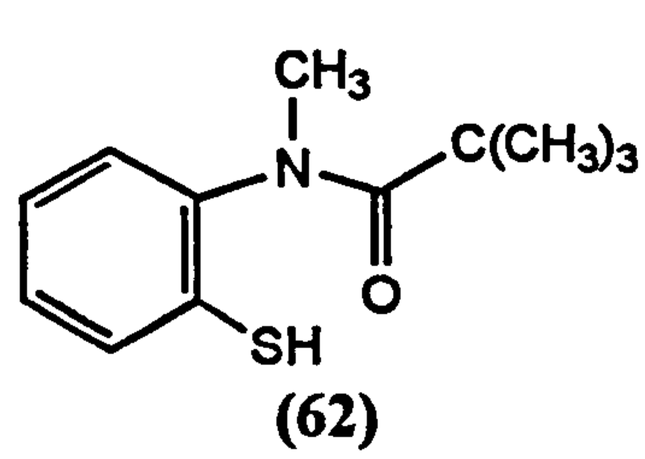
4.2.4 2-*tert*-Butyl-3-methylbenzothiazolium tetrafluoroborate (40) as a mediator



(40)

As well as singlets for the sulfide and sulfoxide at 2.4 and 2.7 ppm respectively, the ^{1}H NMR spectrum of the crude reaction mixture revealed two new singlets at 1.1 ppm and 3.2 ppm. Signals corresponding to the mediator would be expected at 1.8 ppm and 4.5 ppm, but were not present. In the mass spectrum there was a peak at m/z = 222.

The conclusion that *N*-(2-mercapto-phenyl)-*N*-methyl-2',2'-dimethylpropionamide is formed from the mediator during the oxidation was confirmed by comparison of the spectral data from an authentic sample to that for the crude reaction mixture. The HPLC chromatogram also supported this conclusion, with a peak eluting with same retention time as the authentic compound.



(62)

4.3 The use of other mediators for the oxidation of thioanisole

The two benzimidazolium tetrafluoroborate salts **(42)** and **(43)** that were previously synthesised were assessed as catalytic mediators for the oxidation of thioanisole under the standard set of reaction conditions **(Scheme 4.1)**. Also assessed were 1,2,3,3-tetramethyl-3*H*-indoleninium tetrafluoroborate and 3-*t*-butyl-1, 2-benzisothiazole-1,1-dioxide **(65)**. The neutral compound **(65)** has previously been used in a catalytic manner to oxidise sulfides almost quantitatively in conjunction with alkaline hydrogen peroxide.[15]

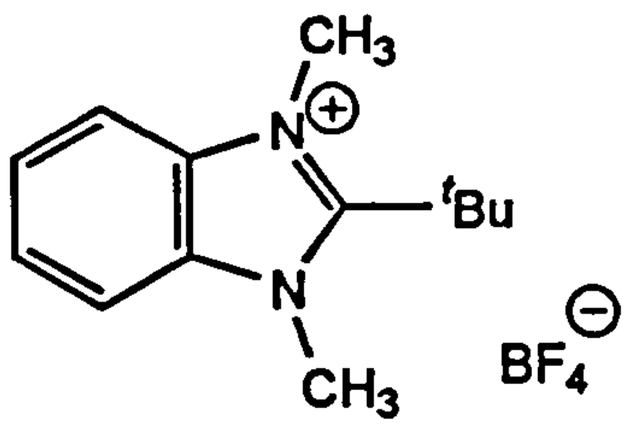
Aliquots were taken at appropriate time intervals and analysed by reversed-phase HPLC (using biphenyl as an internal standard). The amount of phenyl methyl sulfoxide formed after 24 and 48 hours is shown for each mediator in **Table 4.3**.

Table 4.3 The oxidation of thioanisole by other mediators

Entry	Compound	% Conversion (24 hours)	% Conversion (48 hours)
1	**(42)**	8	13
2	**(43)**	3	9
3	**(44)**	6	9
4	**(65)**	36	63

% Conversion = no. of moles sulfoxide/ (no. of moles sulfoxide + no. of moles sulfide)

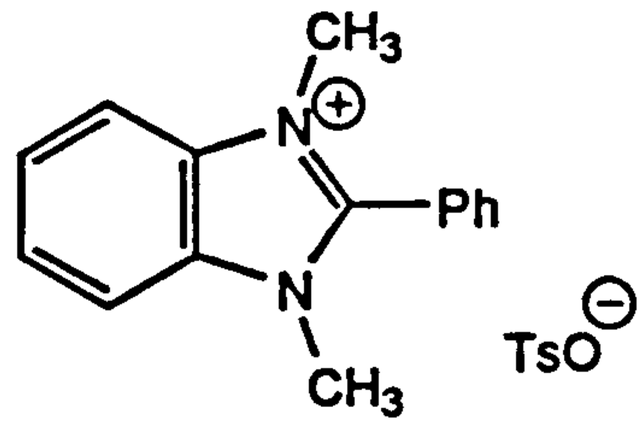
4.3.1 1, 3-Dimethyl-2-*t*-butylbenzimidazolium tetrafluoroborate (42) as a mediator



(42)

This benzimidazolium salt gave only a little enhancement over the uncatalysed oxidation of thioanisole. There are three possible explanations for this: either the salt is extremely unstable under the conditions of the reaction, it does not form an adduct with hydrogen peroxide, or the adduct is not active for the transfer of oxygen to thioanisole. Since no decomposition products were observed either by HPLC or TLC, one can assume that **(42)** is stable under the reaction conditions. As it is likely that any hydroperoxide adduct formed would transfer oxygen to sulfides, it is proposed that no adduct is formed from hydrogen peroxide and **(42)**. This is because the structure of benzimidazolium salts means that the positive charge of the iminium group is split over two nitrogen atoms, decreasing its susceptibility to attack by nucleophiles.

4.3.2 1, 3-Dimethyl-2-phenylbenzimidazolium tosylate (43) as a mediator

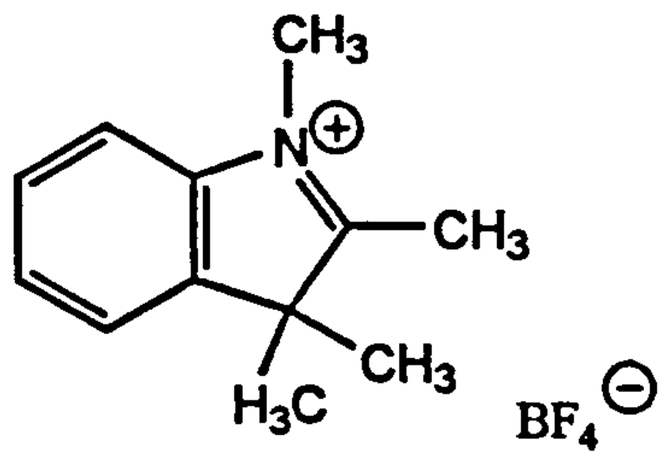


(43)

This benzimidazolium salt gave no enhancement over the uncatalysed oxidation of thioanisole and is slightly less active than the 2-*t*-butyl derivative. Again, no decomposition products were observed either by HPLC or TLC, so the mediator is not very active because the delocalisation of the positive charge over the two equivalent nitrogen atoms means the salt does not react with hydrogen peroxide.

Assuming that the phenyl and *t*-butyl groups are sterically similar, the small difference in activity is probably caused by conjugation of the aromatic group to the iminium moiety. This further reduces the susceptibility of the iminium bond to attack by nucleophiles, such as hydrogen peroxide.

4.3.3 1,2,3,3-Tetramethyl-3*H*-indoleninium tetrafluoroborate (44) as a mediator

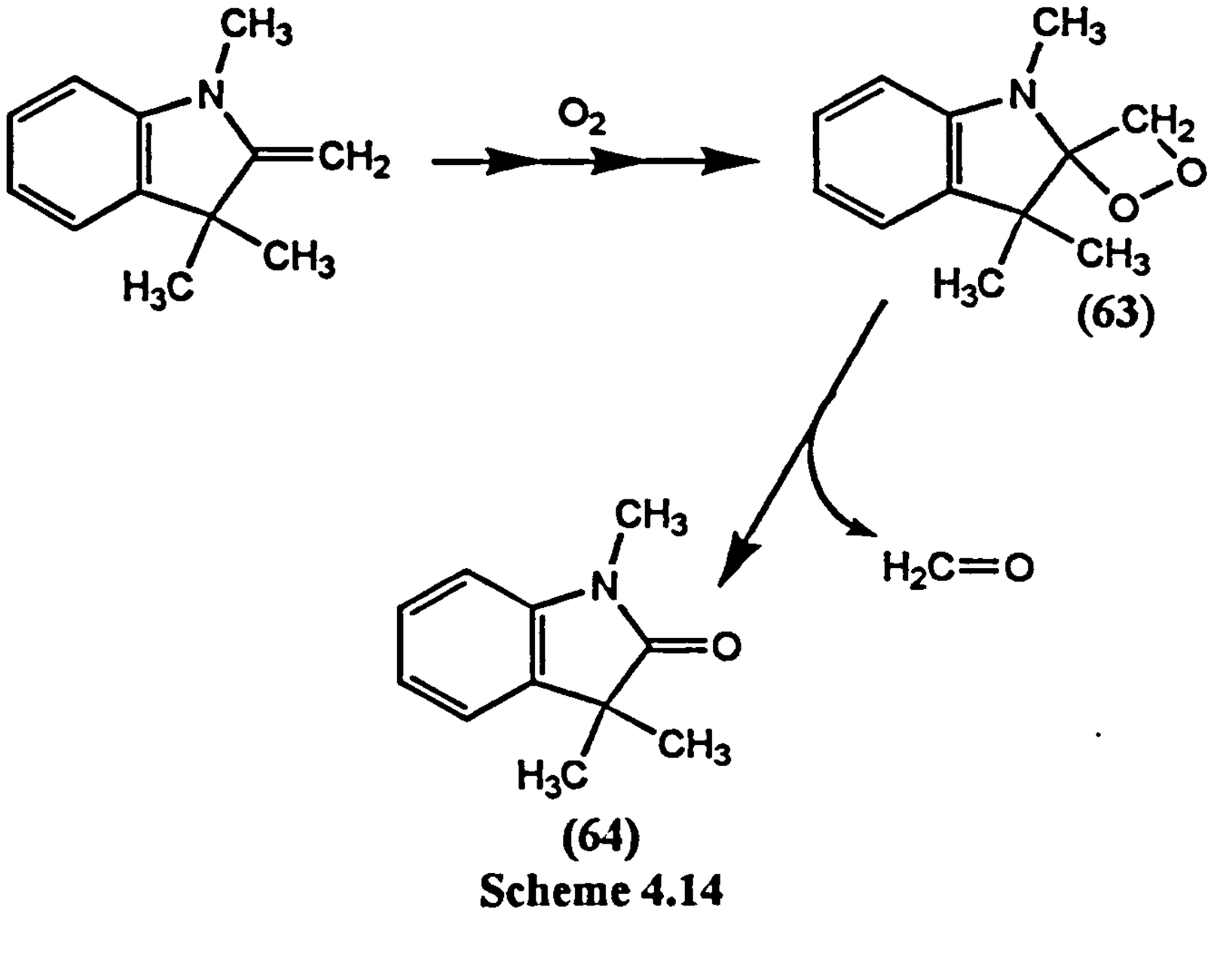


(44)

This indoleninium salt gave no significant enhancement over the uncatalysed oxidation of thioanisole (entry 3). A ^{1}H NMR spectrum of the crude reaction mixture revealed peaks corresponding to the sulfide and sulfoxide at 2.4 (CH_3-S) and 2.7 ppm (CH_3-SO) and two new resonances: a singlet at 1.3 ppm and a singlet at 3.2 ppm. There were no signals corresponding to the mediator (singlets at 1.5 (2 x CH_3), 2.9 (CH_3) and 4.1 ppm (N-CH_3)). In the mass spectrum there was a peak at m/z = 175. By comparison to the literature values,[16] both support the conclusion that 1,3,3 trimethyloxindole **(64)** is formed from the mediator during the oxidation. This compound was also detected in the HPLC chromatogram.

Robinson has showed that when 1,2,3,3-tetramethyl-3*H*-indoleninium iodide is treated with base 1,3,3-trimethyl-2-methyleneindoline is produced and this compound is subsequently converted to 1,3,3 trimethyloxindole **(64)** upon exposure to air.[17] The mechanism he proposed for this autoxidation involves the addition of (triplet)

dioxygen across the methylene group to give **(63)** which dissociates into 1,3,3 trimethyloxindole and formaldehyde **(Scheme 4.14)**.



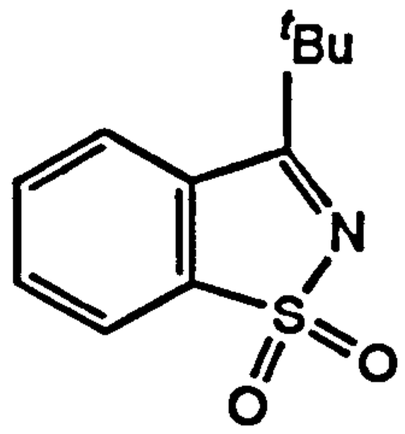
(63)

(64)

Scheme 4.14

4.3.4 3-*t*-Butyl-1, 2-benzisothiazole-1,1-dioxide (65) as a mediator

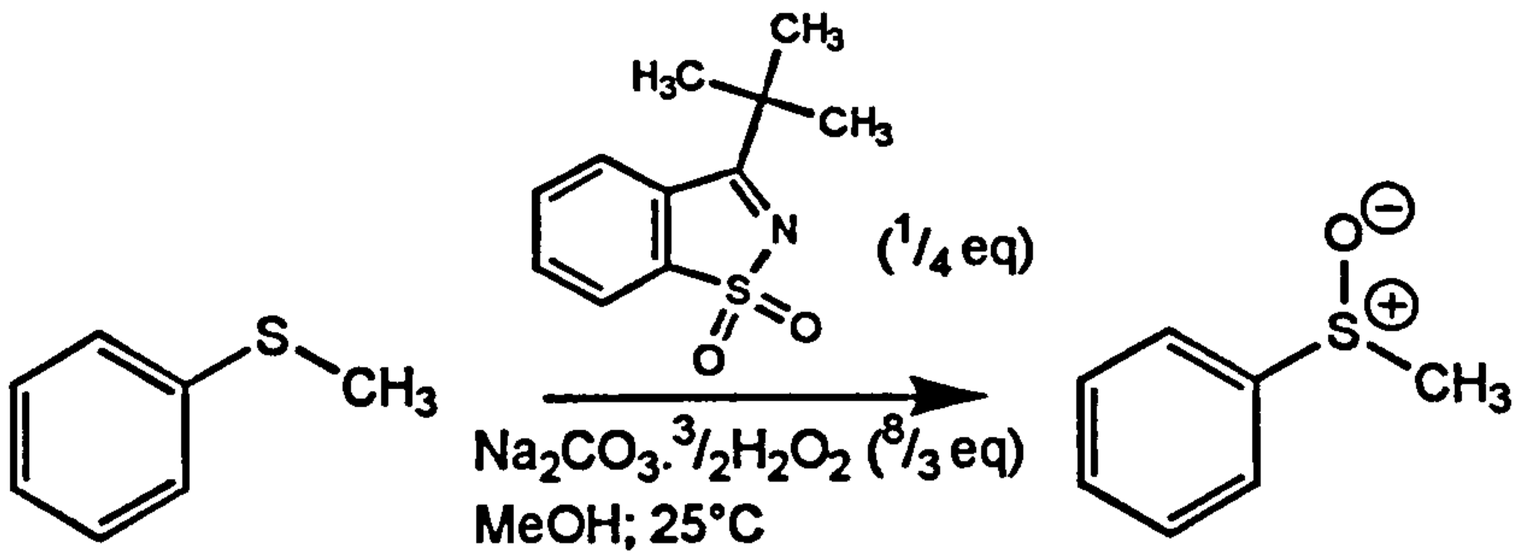
3-*t*-Butyl-1, 2-benzisothiazole-1,1-dioxide **(65)** has been previously shown to oxidise methyl *p*-tolyl sulfide with aqueous hydrogen peroxide under basic conditions. Although stoichiometric quantities were required to achieve good rates of reaction, the oxidation was shown to be catalytic.



(65)

This compound was tested as a mediator for the oxidation of thioanisole under the standard reaction conditions with sodium percarbonate as the oxidant **(Scheme 4.15)**. The yield of sulfoxide was 36 % after 24 hours, but the reaction continued at the same rate and 63 % of sulfoxide was produced after 48 hours, indicating that this sulfonylimine is acting in a catalytic fashion. The concentration of the mediator was

confirmed to be the same at the beginning and end of reaction by comparison of the HPLC chromatographs (the integrals of the peaks corresponding to the mediator were equal).



Scheme 4.15

4.4 Heterogeneous oxidation at a higher temperature

Some of the 2-substituted benzoxazolium salts were used as mediators of oxygen transfer at the higher temperature of 40°C. The reactions were carried out under conditions identical to those above (**Scheme 4.1**), apart from the change in temperature. The conversion of sulfide to sulfoxide after 24 and 48 hours is shown in **Table 4.4**. No sulfone was formed at this temperature. The initial rates of thioanisole consumption and sulfoxide formation are shown in **Table 4.5**. The rates were calculated using linear regression analysis by fitting the data to 2nd order polynomial equations.

Table 4.4 The oxidation of thioanisole by 2-substituted benzoxazolium salts at 40°C

R	Y	Compound	% Conversion (24 hours)	% Conversion (48 hours)
Uncatalysed reaction		n.a.	12	24
H	BF_4	**(35)**	50	66
Cl	BF_4	**(41)**	70	93
Ph	BF_4	**(36)**	38	54
t-Bu	BF_4	**(37)**	52	71

% Conversion = no. of moles sulfide consumed/ initial no. of moles sulfide

Figure 4.2 Graph To Show Production Of Sulfoxide At 40°C By Compounds (41) and (37)

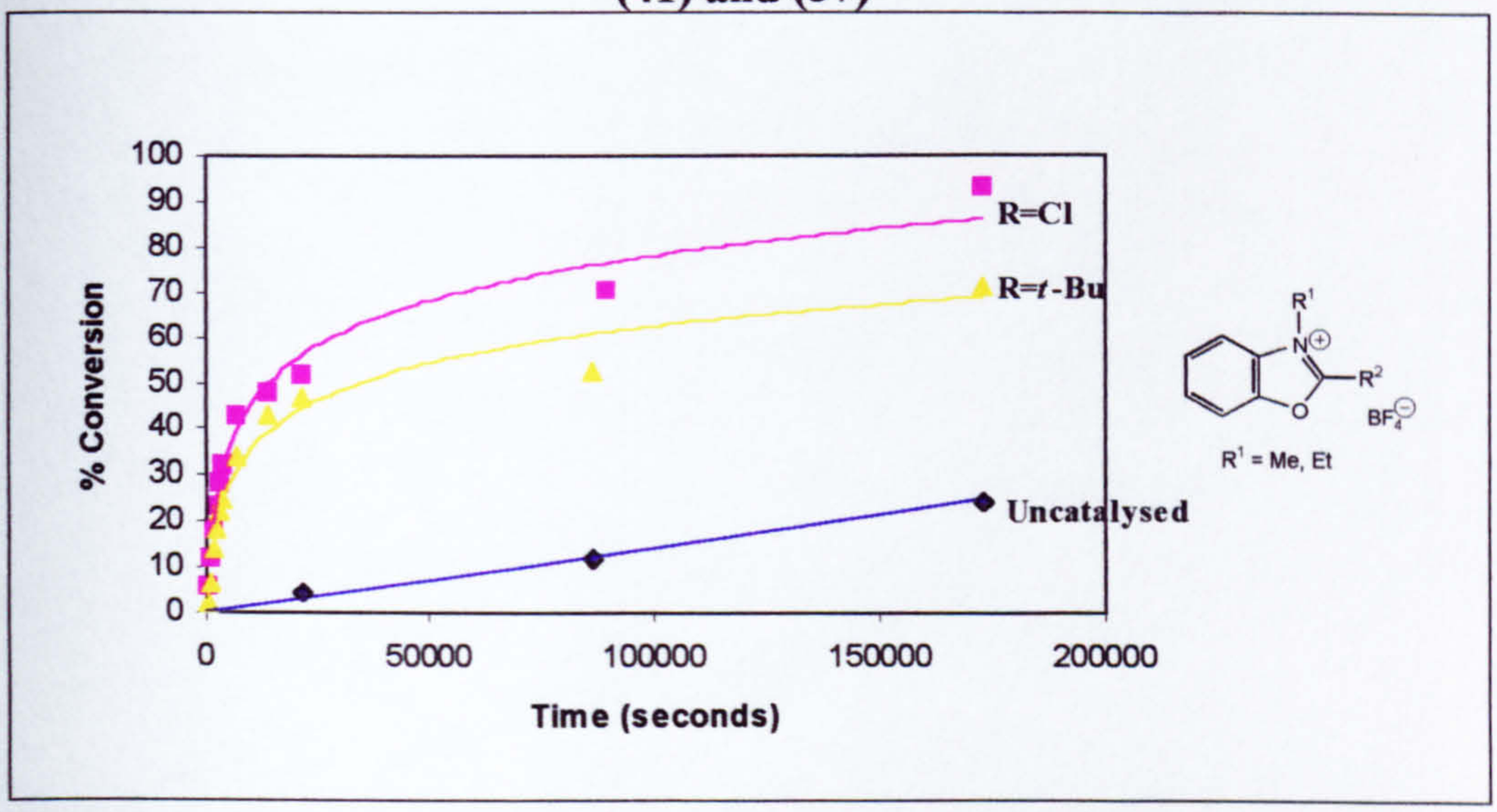
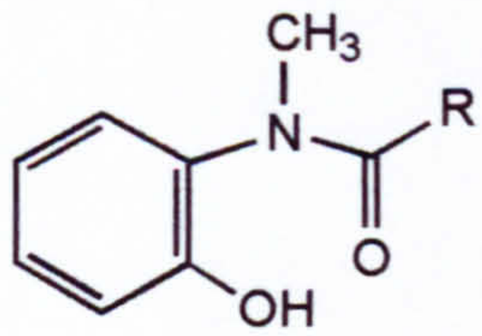


Table 4.5 Initial rates of sulfide consumption and sulfoxide production at 40°C

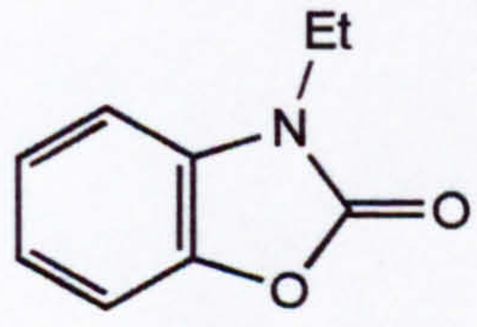
Entry	Compound	Sulfide loss/ $mol.L^{-1}s^{-1}$	R^2	Sulfoxide production/ $mol.L^{-1}s^{-1}$	R^2
1	n.a.	$4.1x10^{-7}$	0.994	$4.1x10^{-7}$	0.984
2	**(35)**	$1.2x10^{-5}$	0.991	n.d.	-
3	**(41)**	$2.7x10^{-5}$	0.994	$3.2x10^{-5}$	0.995
4	**(36)**	$8.8x10^{-6}$	0.981	n.d.	-
5	**(37)**	$1.9x10^{-5}$	0.994	$2.0x10^{-5}$	0.974

$[P] = 17$; $[S]_0 = 268$; $[M]_0 = 67$ $mmol.L^{-1}$

Inspection of the ^1H NMR, mass spectra and HPLC chromatograms of the crude reaction mixtures confirmed that the mediators are converted to the same products that were observed at 25°C. The 2-alkyl/ aryl benzoxazolium salts form the corresponding *o*-amidophenols **(66)** and 2-chloro-3-ethylbenzoxazolium tetrafluoroborate is converted to 3-ethylbenzoxazolinone **(50)**.



(66)



(50)

4.4.1 Discussion

In the uncatalysed reaction (entry 1) 12 % of thioanisole is converted to phenyl methyl sulfoxide after 24 hours; the concentration-time plot is linear over the course of the reaction and continues at this rate for the next 24 hours (**Figure 4.2**).

The 2-alkyl and 2-phenyl benzoxazolium salts that gave only one equivalent of sulfoxide at 25°C produce more than one mole of sulfoxide per mole of mediator added at this temperature. This means that turnover and thus catalysis is occurring at this temperature.

2-Chloro-3-ethylbenzoxazolium tetrafluoroborate **(41)** produces more than twice a molar equivalent of sulfoxide within 24 hours (taking into account that produced in the uncatalysed reaction) and sulfoxide is produced almost quantitatively after 48 hours. This mediator produces the most phenyl methyl sulfoxide of all the benzoxazolium salts tested at this temperature (**Table 4.4**); the rate of conversion of sulfide to sulfoxide is also fastest for this compound (**Table 4.5**).

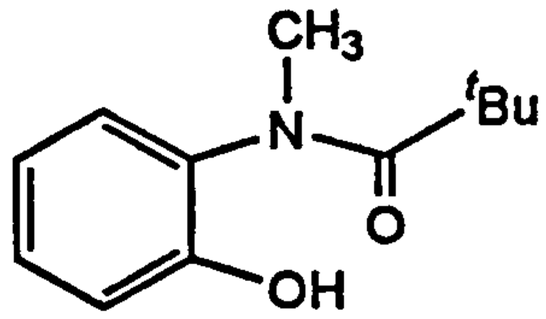
Compound **(36)** produces the least phenyl methyl sulfoxide and has the slowest rate of sulfoxide production. This is probably because the 2-phenyl group is conjugated to the iminium bond, reducing its susceptibility to nucleophilic attack by hydrogen peroxide. Compounds **(35)** and **(37)** produce intermediate amounts of sulfoxide, with compound **(37)** having a faster rate and giving slightly more sulfoxide. The 2-*t*-butyl group increases the resistance of compound **(37)** to hydrolysis, so it is more persistent under the reaction conditions than **(35)** and thus produces more sulfoxide overall.

For most of the benzoxazolium salts (R = H, Ph, *t*-Bu) the reaction begins quickly, but then tails off to a rate slightly faster than the uncatalysed reaction for the second 24 hours; this is exemplified by compound **(37)**. For compound **(41)** the rate of reaction settles to a rate that is more than twice as fast as the uncatalysed reaction **(Figure 4.2)**

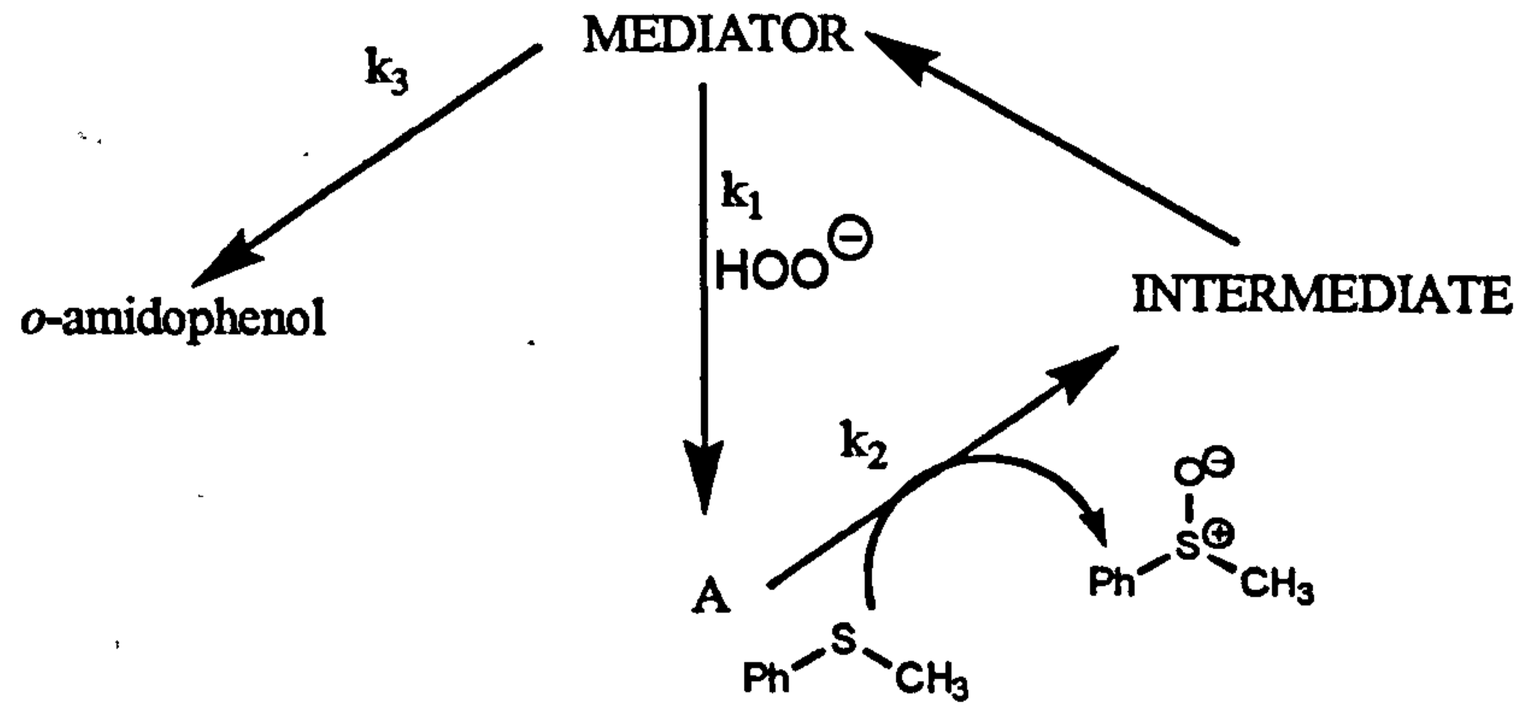
The fact that turnover occurs at this temperature means that the oxidation of thioanisole by the 2-alkyl and 2-phenyl benzoxazolium salts is occurring catalytically. This means that one of the mechanisms (**Scheme 4.7**) proposed earlier can be ruled out since the amounts of sulfoxide produced are too large to be accounted for by a stoichiometric reaction.

Since *N*-(2-hydroxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide **(52)** is able to mediate the oxidation of thioanisole, one must consider the possibility that the *o*-amidophenols formed are converted under the reaction conditions to the corresponding benzoxazolium salts. This leaves two likely mechanisms, depending on

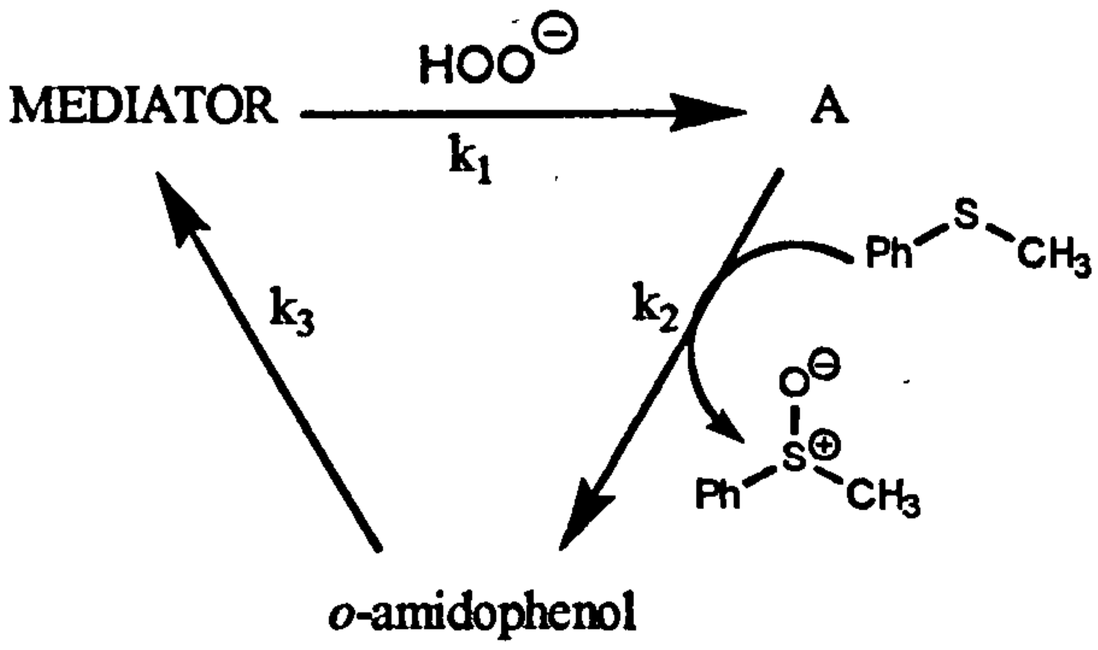
whether the active oxidant is converted to the benzoxazolium salt **(Scheme 4.16)** or *o*-amidophenol **(Scheme 4.17)** in the oxygen transfer process. This will be investigated further in the next chapter.



(52)



Scheme 4.16



Scheme 4.17

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Chapter 5

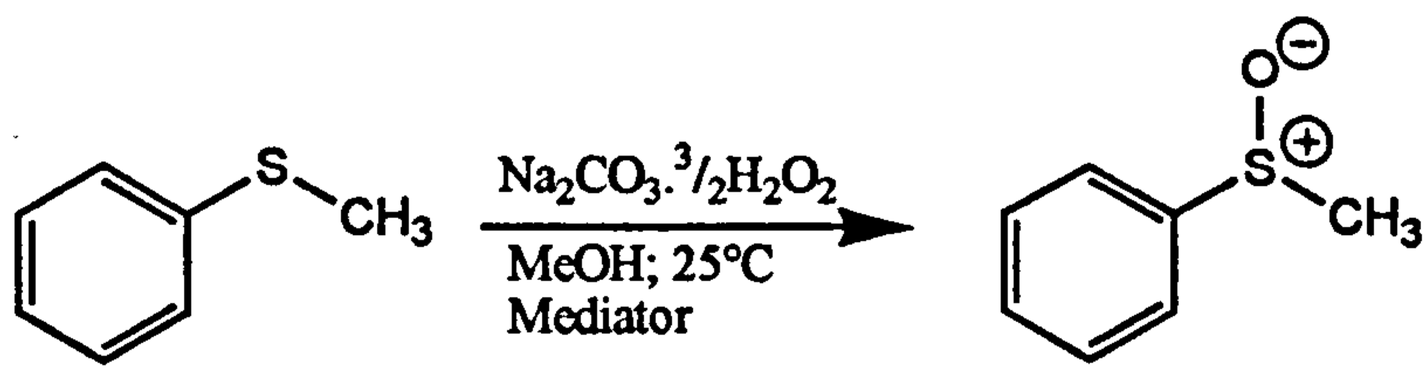
Investigation Of The Mechanism Of Oxidation

5.1 Investigation of heterogeneous reactions

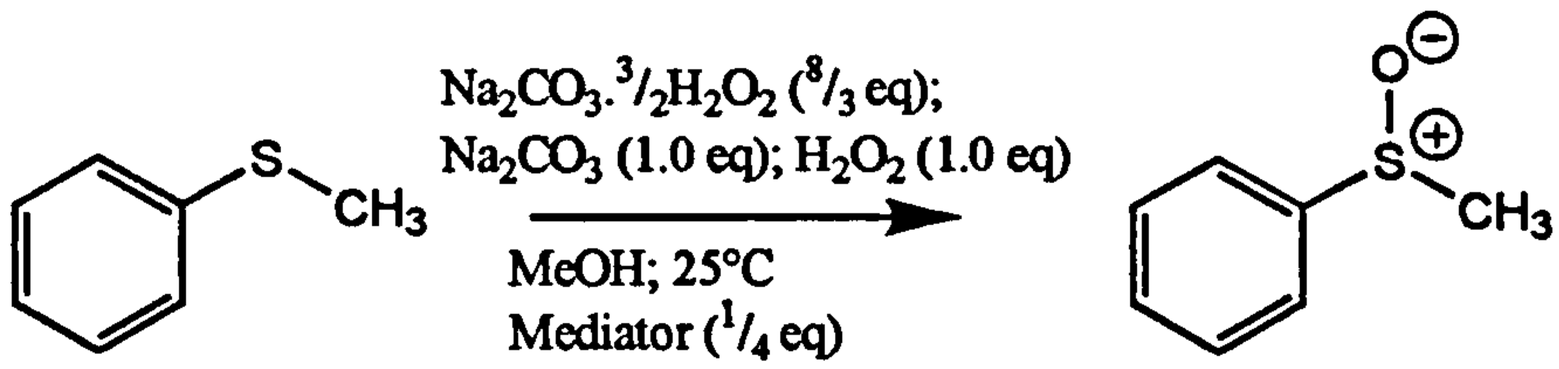
To assess the influence of each component upon the rate of the reaction, the oxidation of thioanisole was performed with some of the 2-substituted benzoxazolium salts as mediators, using different initial concentrations of each reaction component. Since sodium percarbonate is a solid reagent that remains undissolved in these reactions, it will have a constant concentration in solution.

The conditions used were the same as those for the standard reaction (**Scheme 5.1**) apart from the changes in the initial concentrations of the reactants. For entries 1-3 (**Tables 5.2-5.11**), 4 equivalents of hydrogen peroxide (with respect to sulfide) were added to the reaction in the form of solid sodium percarbonate, maintaining a constant concentration of 0.017 $mol.L^{-1}$ for the entire reaction. The concentration of mediator was increased 4 times in entry 2, making its initial concentration the same as thioanisole (0.27 $mol.L^{-1}$). The initial concentration of sulfide was doubled to 0.54 $mol.L^{-1}$in entry 3. In order to increase the concentration of hydrogen peroxide in solution (entry 4; **Tables 5.2-5.11**) it was necessary to add aqueous hydrogen peroxide solution (30 % w/v) and also sodium carbonate to prevent uncatalysed oxidation (**Scheme 5.2**).

The concentrations of hydrogen peroxide in these solutions were determined by firstly preparing the reaction solutions in the absence of the sulfide. Aliquots were then taken and, after the addition of acidified sodium iodide solution, the liberated iodine was titrated against standard sodium thiosulfate solution. These titrations revealed that the concentration of hydrogen peroxide in the standard reaction is 17 $mmol.L^{-1}$ and this increases to 220 $mmol.L^{-1}$ in the case where aqueous hydrogen peroxide is added.



Scheme 5.1



Scheme 5.2

Aliquots were taken at appropriate time intervals and analysed by reversed-phase HPLC (using biphenyl as an internal standard). The concentrations of thioanisole and phenyl methyl sulfoxide against time were plotted for 48 hours. The values for the initial rates were calculated from data points (typically 6) obtained in the initial 60 minutes of the reaction. The data was fitted to a 2nd order polynomial using regression analysis; after differentiation and setting t = 0, the values for the initial rates were obtained.

5.1.1 Uncatalysed reactions

From **Table 5.1**, when the concentration of hydrogen peroxide is increased 13-fold, the initial rate increases by 17-20 times, so the rate of the uncatalysed reaction is approximately proportional to the concentration of hydrogen peroxide. For the standard reaction (**Scheme 5.1**) the concentration of the sulfide decreased almost linearly over the time monitored.

5.1.2 Interpretation of rate laws for the mediated oxidations

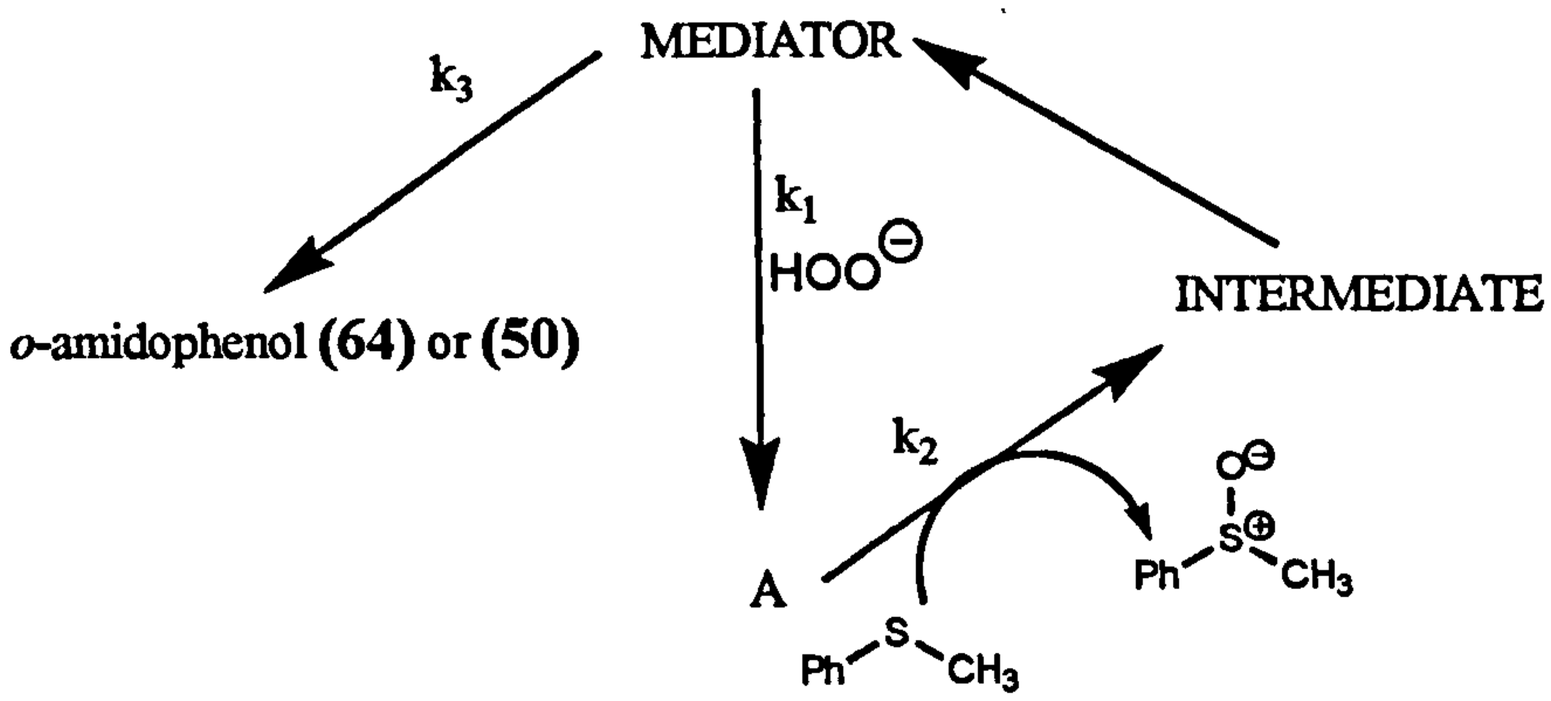
Rate equations were set up for the two mechanisms shown in **Scheme 5.3** and **Scheme 5.4**. The equations were integrated and compared to the data obtained in the heterogeneous reactions in order to shed light on the mechanism of the oxidations (for derivations see chapter 7). In all of the derivations the concentration of hydrogen peroxide is assumed to be a constant since this has been demonstrated by titration.

The case where the sulfide oxidation is catalytic and the mediator is consumed in a separate process (**Scheme 5.3**) leads to expression **[14]**. The assumptions made are that k_3 and k_1 are slow steps and that the depletion of M is a pseudo-first order process (since the concentration of base is a constant because there is undissolved sodium percarbonate).

Table 5.1 Initial rates of sulfide consumption and sulfoxide production in uncatalysed reactions

Entry	$[P]_0$[a] ($mmol.L^{-1}$)	$[S]_0$ ($mmol.L^{-1}$)	$-d[S]/dt$ ($mol.L^{-1}s^{-1}$)	R^2	Relative rate	$d[SO]/dt$ ($mol.L^{-1}s^{-1}$)	R^2	Relative rate	% Conversion (24 hours)
1	17	282	$9.2x10^{-8}$	0.996	1.0	$8.0x10^{-8}$	0.999	1.0	5
2	220	268	$1.6x10^{-6}$	0.867	17	$1.6x10^{-6}$	0.962	20	7

[a]Determined by titration; constant throughout reaction
$[P]_0$-Initial concentration of hydrogen peroxide
$[S]_0$- Initial concentration of thioanisole
$[SO]_0$- Initial concentration of phenyl methyl sulfoxide



Scheme 5.3

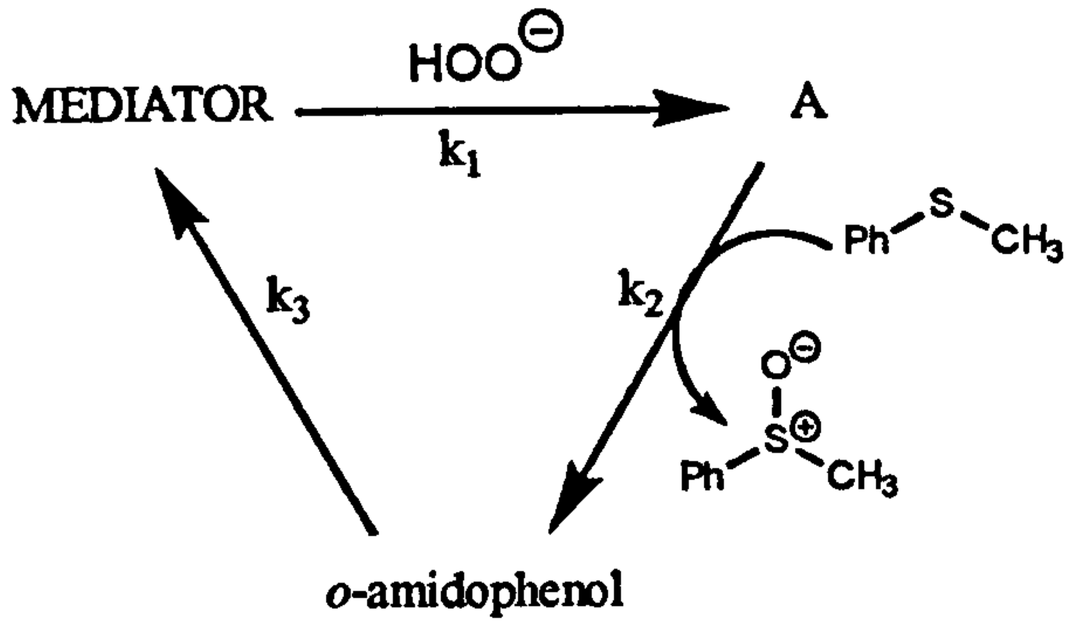
$$ln\ \{[S] - [S]_\infty\} = (-k_3\ t) + \{k_1'\ [M]_0/\ k_3\} \qquad \textbf{[14]}$$

From **[14]** one can see that if **Scheme 5.3** is indeed the actual mechanism of the reaction, then a plot of *ln* $\{[S] - [S]_\infty\}$ against time should be a straight line. The value used for $[S]_\infty$ is the final value obtained for [S] at 172800 s (48 hours). The mechanism shown in **Scheme 5.3** can also lead to the rate expression **[15]**, if one assumes that the decomposed mediator is in equilibrium with M.

$$-\delta[S]/\delta t = k_3\ [P]\ \{([M]_0K)/(K + 1)\} \qquad \textbf{[15]}$$

This expression means that the rate of reaction would be a constant since the concentration of hydrogen peroxide is constant throughout the reaction. Inspection of the concentration-time curves reveals that they are not linear, so this possibility can be ruled out.

The mechanism shown in **Scheme 5.4** produces the following rate expressions. If the reaction is truly catalytic then the rate should be constant over most of the reaction, leading to equation **[16]**. However, if one assumes that k_3 is considerably smaller than k_2 or k_1, then during the initial period of the reaction the formation of sulfide is governed by the rate of formation of the oxygen transfer agent (A), leading to **[17]**. As the reaction proceeds, the concentration of *o*-amidophenol increases relative to the concentration of the benzoxazolium salt and the rate-determining step becomes the reformation of the mediator from the *o*-amidophenol, which will have attained a constant concentration.



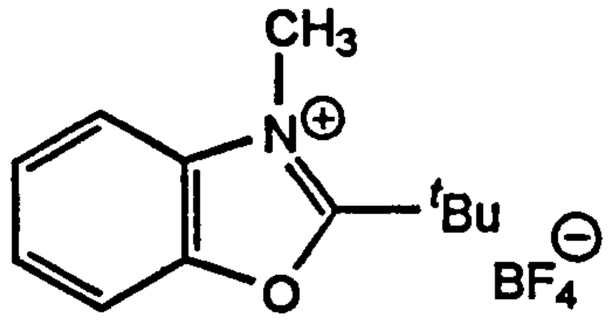
Scheme 5.4

$$[S] = [S]_0 - k' t \qquad [16]$$

$$ln\ \{[M]_0/([M]_0 - \Delta[S])\} = - k't \qquad [17]$$

In all cases the concentration-time data was plotted according to equations **[14]**, **[15]**, **[16]** and **[17]** and the best correlations were noted; typically there were 12 data points in each correlation.

5.1.3 2-*t*-Butyl-3-methylbenzoxazolium tetrafluoroborate (37)



(37)

The rate of reaction increases proportionally with the concentration of mediator, indicating that the reaction is first order in iminium salt (**Table 5.2**; entry 2). Increasing the initial sulfide concentration does not affect the rate, so the oxidation is independent of thioanisole concentration. The rate is doubled when the concentration of hydrogen peroxide is increased 13-fold and so the rate apparently does not increase proportionally with hydrogen peroxide concentration.

The data from **Table 5.2** (entries 1-4) can be fitted to equation **[14]** with good correlation ($R^2 = 0.944$-0.981). This supports the postulate that the mechanism of the reaction is that shown in **Scheme 5.3** (with k_3 small) i.e. the mediator acts catalytically and is decomposed in a separate pathway forming the *o*-amidophenol. None of the other integrated rate equations successfully describes the data obtained.

Table 5.2 Initial rates of sulfide consumption and sulfoxide production mediated by compound (37)

Entry	$[P]_0$[a] ($mmol.L^{-1}$)	$[S]_0$ ($mmol.L^{-1}$)	$[M]_0$ ($mmol.L^{-1}$)	-d[S]/dt ($mol.L^{-1}s^{-1}$)	R^2	Relative rate	d[SO]/dt ($mol.L^{-1}s^{-1}$)	R^2	Relative rate
1	17	282	66	$1.1x10^{-5}$	0.983	1.0	$1.5x10^{-5}$	0.971	1.0
2	17	268	271	$4.5x10^{-5}$	0.999	4.1	$5.4x10^{-5}$	0.982	3.6
3	17	537	66	$1.2x10^{-5}$	0.971	1.1	$1.1x10^{-5}$	0.984	0.7
4	220	268	67	$2.1x10^{-5}$	0.971	1.9	n.d.		

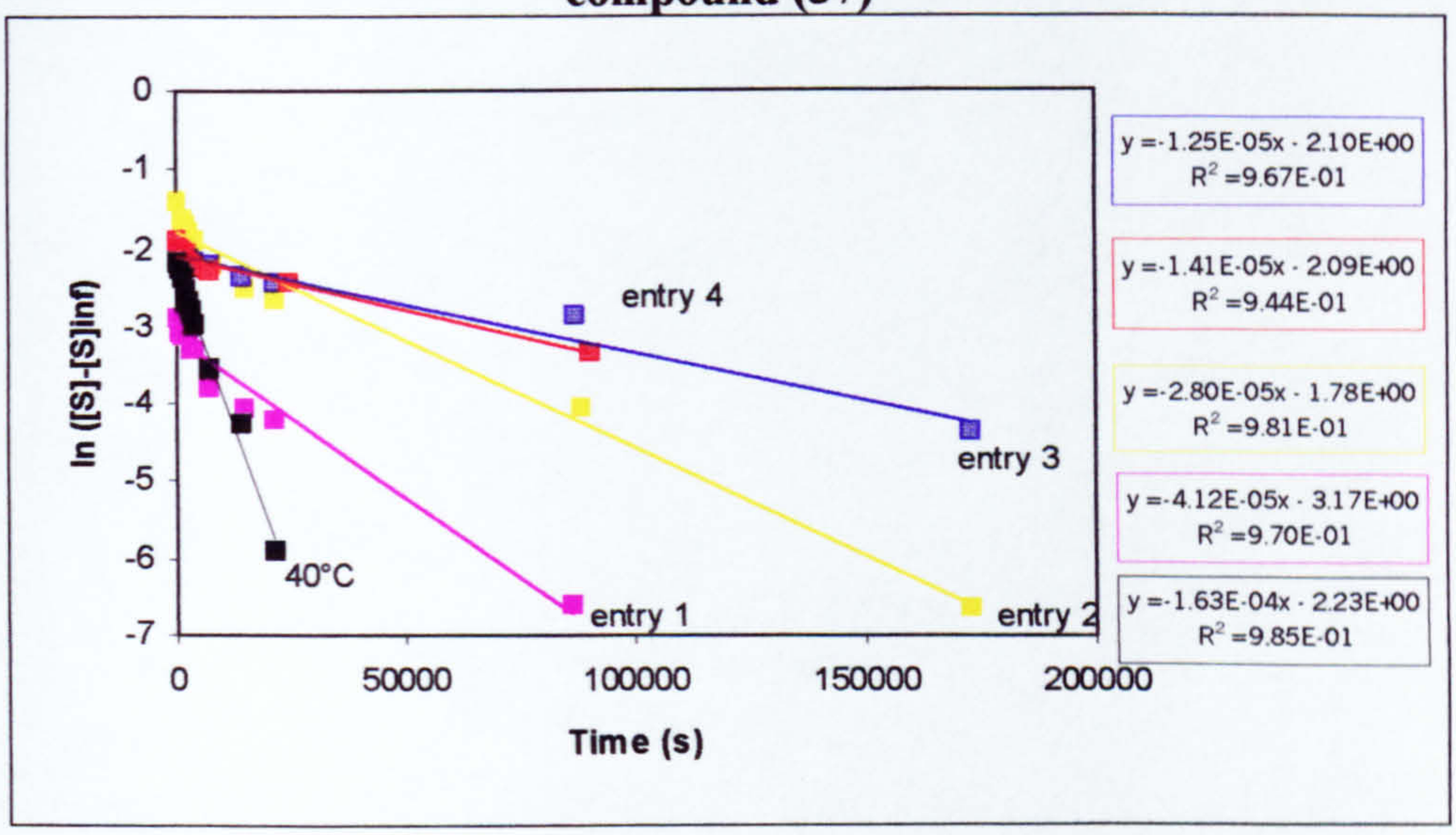
[a] Determined by titration; constant throughout reaction

Table 5.3 Conversion of sulfide mediated by compound (37)

Entry	Constant Concentration [P] ($mmol.L^{-1}$)	$[S]_0$ ($mmol.L^{-1}$)	$[M]_0$ ($mmol.L^{-1}$)	% Conversion To Sulfoxide (24 hours)	% Conversion To Sulfoxide (48 hours)
1	17	282	66	29	32
2	17	268	271	80	89
3	17	537	66	18	23
4	220	268	67	47	63

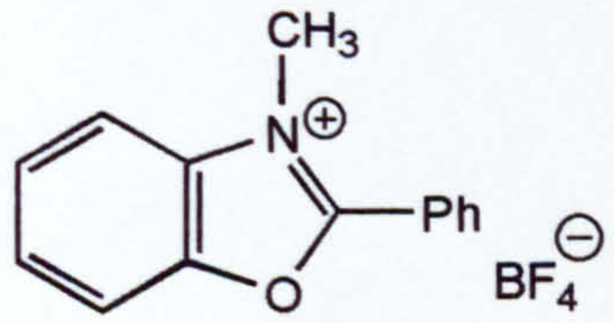
At the higher temperature of 40°C (**Section 4.4**) the data is also adequately described by equation **[14]** ($R^2 = 0.985$). There is no correlation with any of the other equations. This implies that the reaction follows the same mechanism at this temperature.

Figure 5.1 Correlation of *ln* {[S] – [S]$_\infty$} with time for oxidations mediated by compound (37)



Thioanisole is 80 % converted to phenyl methyl sulfoxide after 24 hours in the case where the mediator is present in a stoichiometric quantity (**Table 5.3**, entry 2). Extra hydrogen peroxide increases the conversion of thioanisole to 47 % (entry 4).

5.1.4 2-Phenyl-3-methylbenzoxazolium tetrafluoroborate (36)



(36)

The initial rate of reaction decreases slightly with increased sulfide concentration and seems to be independent of hydrogen peroxide concentration (**Table 5.4**). The reaction appears to be first order in mediator since the rate increases almost proportionally to its concentration.

Table 5.4 Initial rates of sulfide consumption and sulfoxide production mediated by compound (36)

Entry	$[P]_0$[a] ($mmol.L^{-1}$)	$[S]_0$ ($mmol.L^{-1}$)	$[M]_0$ ($mmol.L^{-1}$)	$-d[S]/dt$ ($mol.L^{-1}s^{-1}$)	R^2	Relative rate	$d[SO]/dt$ ($mol.L^{-1}s^{-1}$)	R^2	Relative rate
1	17	268	67	$1.5x10^{-5}$	0.990	1.0	$1.6x10^{-5}$	0.975	1.0
2	17	268	269	$5.3x10^{-5}$	0.937	3.5	$4.5x10^{-5}$	0.993	2.8
3	17	537	67	$1.0x10^{-5}$	0.979	0.7	$1.2x10^{-5}$	0.988	0.8
4	220	268	68	$1.5x10^{-5}$	0.986	1.0	n.d.	-	-

[a] Determined by titration; constant throughout reaction

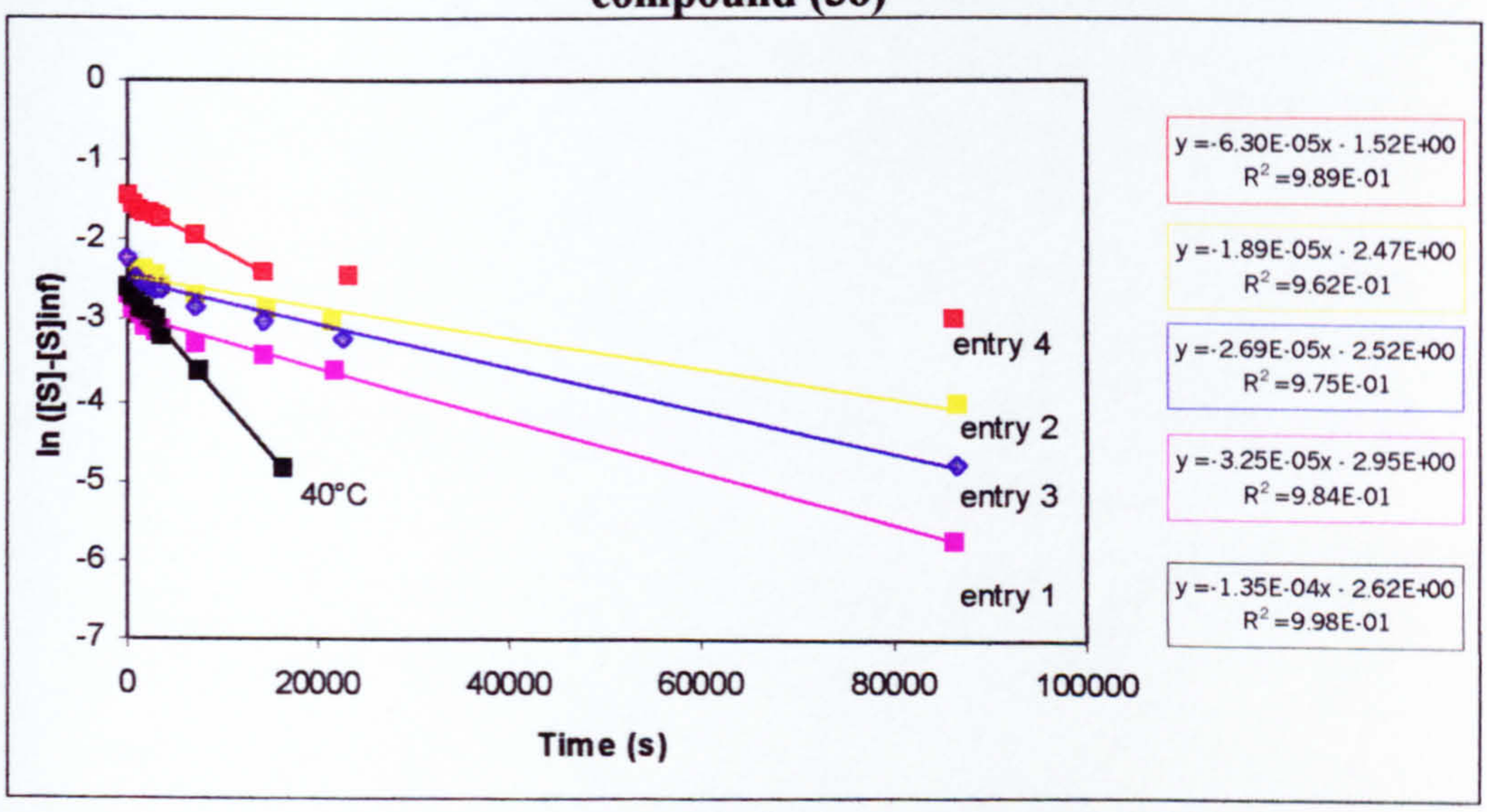
Table 5.5 Conversion of sulfide mediated by compound (36)

Entry	Constant Concentration [P] ($mmol.L^{-1}$)	$[S]_0$ ($mmol.L^{-1}$)	$[M]_0$ ($mmol.L^{-1}$)	% Conversion To Sulfoxide (24 hours)	% Conversion To Sulfoxide (48 hours)
1	17	268	67	32	37
2	17	268	269	51	59
3	17	537	67	14	17
4	220	268	68	70	92

The concentration-time data from **Table 5.4** (entries 1, 2, 3) give a good correlation with equation **[14]** (R^2 = 0.962-0.989). For entry 4, the last 2 time points (23400 and 86400 s) do not fit the correlation established earlier in the reaction (**Scheme 5.2**). Inspection of the concentration-time curve suggests that the rate is higher than expected at this point; this implies that the concentration of mediator is higher than expected from the proposed mechanism, so perhaps it can be reformed from the decomposition products in this case.

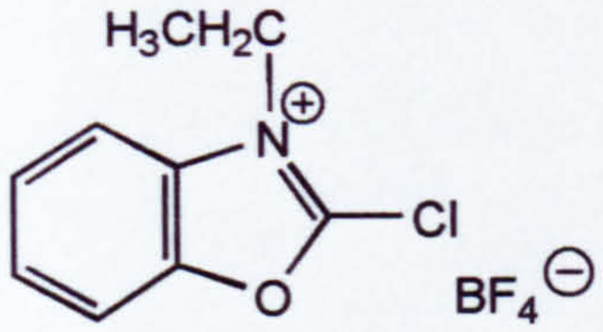
The data obtained at the higher temperature of 40°C (**Section 4.4**) shows excellent correlation between *ln* {[S] – $[S]_\infty$} and time (R^2 = 0.998); this implies that the reaction follows the pathway shown in **Scheme 5.3**. An important point to note is that the rate of the oxidation mediated by **(36)** is slower at this temperature ($-\delta[S]/\delta t = 8.8 \times 10^{-6}$), in contrast with the normal behaviour of simple reactions, and this indicates a complex mechanism of several steps.

Figure 5.2 Correlation of *ln* {[S] – $[S]_\infty$} with time for oxidations mediated by compound (36)



Increasing the concentration of mediator increases the conversion of thioanisole to 50 % (**Table 5.5**, entry 2). When the concentration of hydrogen peroxide is increased, the sulfide conversion to sulfoxide is 70 % in 24 hours (entry 4), which is the highest conversion for the mediators tested. The conversion is increased to 92 % over the next 24 hours; this indicates that significant quantities of the mediator are still present at this point in the reaction.

5.1.5 2-Chloro-3-ethylbenzoxazolium tetrafluoroborate (41)



(41)

The rate of reaction is apparently independent of both sulfide and hydrogen peroxide concentration, since the rate does not increase when higher initial concentrations of these components are used (**Table 5.6**). When the initial concentration of mediator is increased the rate seems to increase proportionally.

It has been shown that compound **(50)**, the hydrolysis product of **(41)**, does not mediate the reaction and so the mechanism shown in **Scheme 5.4** can be ruled out. The concentration time profiles (**Table 5.6**, entries 1-4) all show good to excellent correlation of *ln* $\{[S] - [S]_\infty\}$ with time (R^2 = 0.960-0.998). This indicates that the likely mechanism of the reaction is that shown in **Scheme 5.3** i.e. the mediator is able to act catalytically in the oxidation, but is slowly decomposed in another process. The reaction carried out at 40°C does not correlate with **[14]** or any of the other integrated rate equations.

Figure 5.3 Correlation of *ln* $\{[S] - [S]_\infty\}$ with time for oxidations mediated by compound (41)

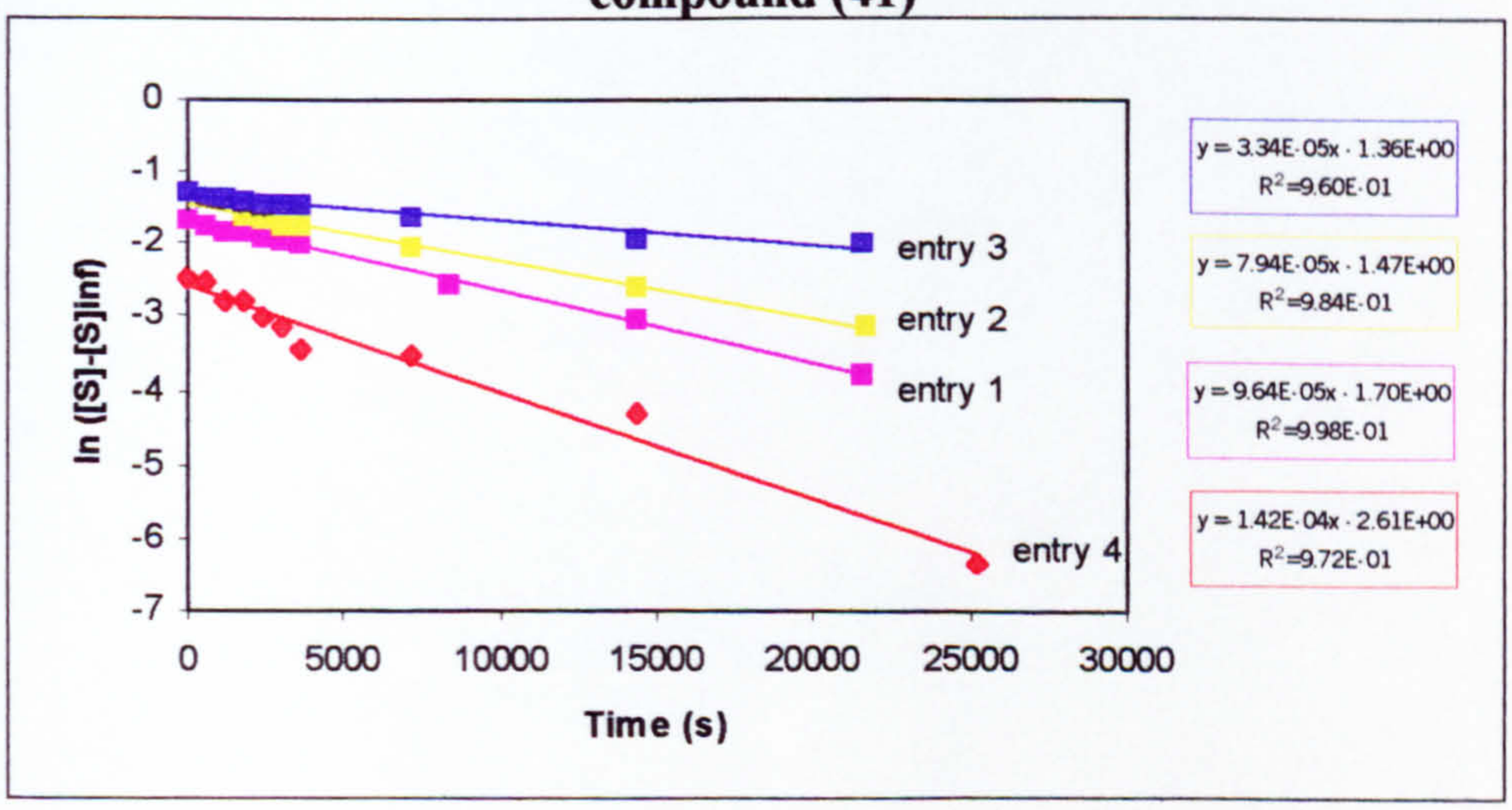


Table 5.6 Initial rates of sulfide consumption and sulfoxide production mediated by compound (41)

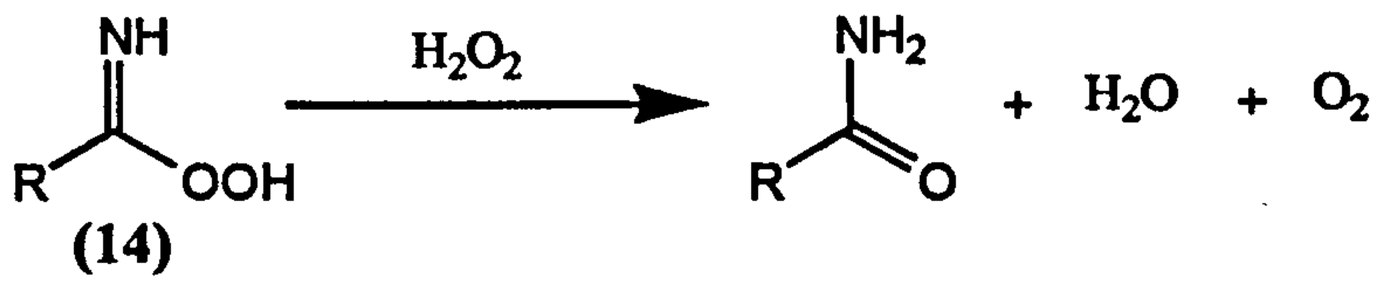
Entry	$[P]_0$[a] ($mmol.L^{-1}$)	$[S]_0$ ($mmol.L^{-1}$)	$[M]_0$ ($mmol.L^{-1}$)	-d[S]/dt ($mol.L^{-1}s^{-1}$)	R^2	Relative rate	d[SO]/dt ($mol.L^{-1}s^{-1}$)	R^2	Relative rate
1	17	282	68	$2.2x10^{-5}$	0.981	1.0	$2.0x10^{-5}$	0.992	1.0
2	17	268	266	$5.8x10^{-5}$	0.996	2.6	$6.1x10^{-5}$	0.993	3.1
3	17	564	74	$1.8x10^{-5}$	0.980	0.8	$1.2x10^{-5}$	0.991	0.6
4	220	268	68	$1.3x10^{-5}$	0.975	0.6	n.d.	-	-

[a] Determined by titration; constant throughout reaction

Table 5.7 Conversion of sulfide mediated by compound (41)

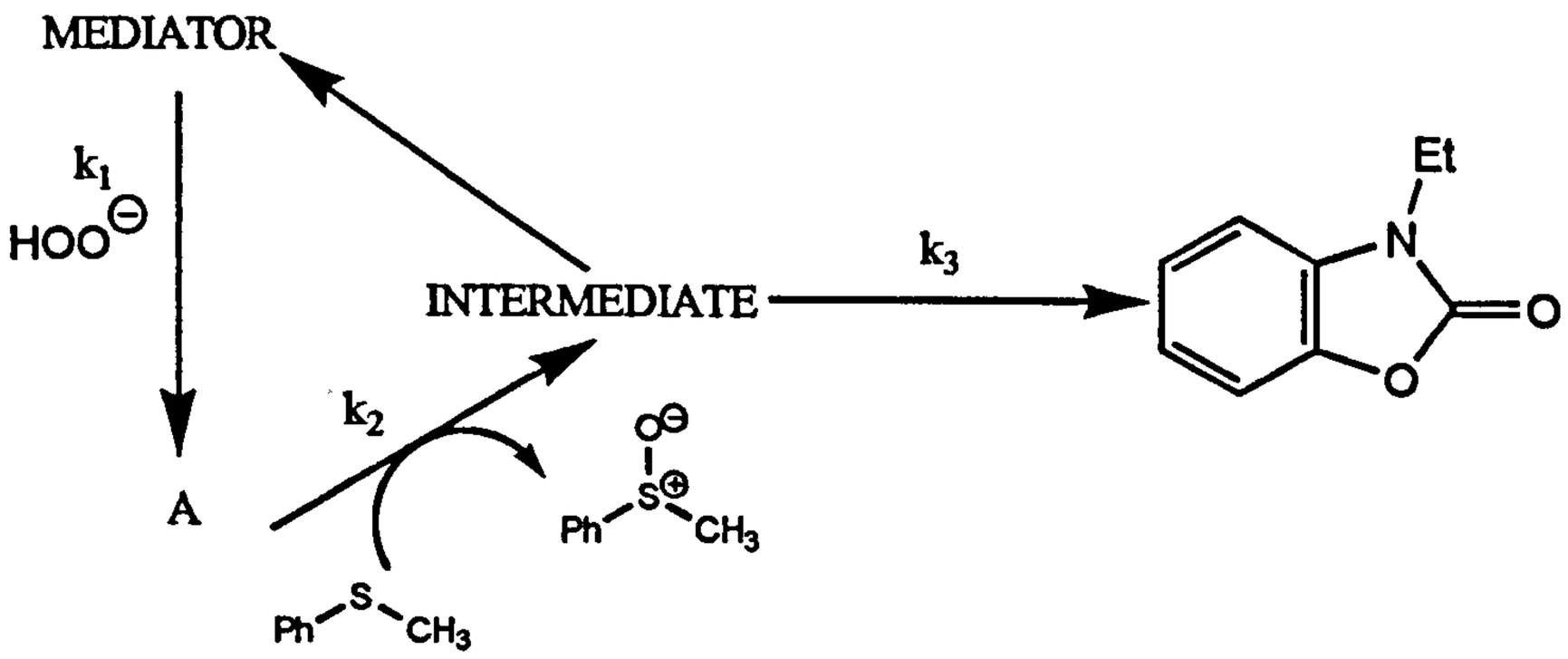
Entry	Constant Concentration [P] ($mmol.L^{-1}$)	$[S]_0$ ($mmol.L^{-1}$)	$[M]_0$ ($mmol.L^{-1}$)	% Conversion To Sulfoxide (24 hours)	% Conversion To Sulfoxide (48 hours)
1	17	282	68	66	n.d.
2	17	268	266	98	99
3	17	564	74	31	39
4	220	268	68	34	37

In the case where equimolar quantities of mediator and sulfide were employed (**Table 5.7**, entry 2), the sulfide is totally converted to sulfoxide within 24 hours. When extra hydrogen peroxide was employed (entry 4), the conversion of thioanisole was decreased, indicating that the decomposition of the mediator may be accelerated with increased hydrogen peroxide concentration. It has been postulated that intermediates such as compound **(14)** are able to oxidise hydrogen peroxide, liberating oxygen gas (Radziszewski oxidation).[1,2] It has been shown that when the concentration of hydrogen peroxide is kept low, this side reaction is minimised. For entries 1, 2 & 3, where the concentration of hydrogen peroxide is low, more sulfoxide is produced at a faster rate.



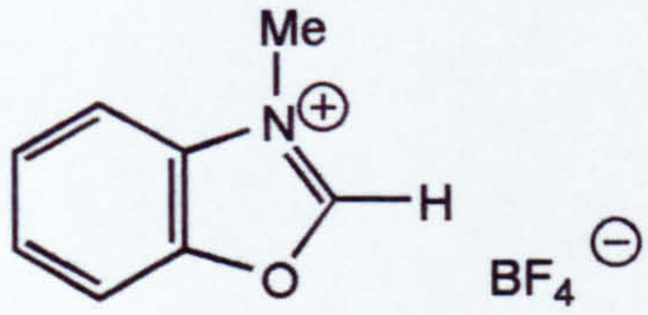
Scheme 5.5

It can be shown that if the reaction mechanism is as shown in **Scheme 5.6**, i.e. the intermediate decomposes rather than the mediator, then the integrated rate equation is very similar to **[14]** and cannot be distinguished from the mechanism shown in **Scheme 5.3**.



Scheme 5.6

5.1.6 3-Methylbenzoxazolium tetrafluoroborate (35)

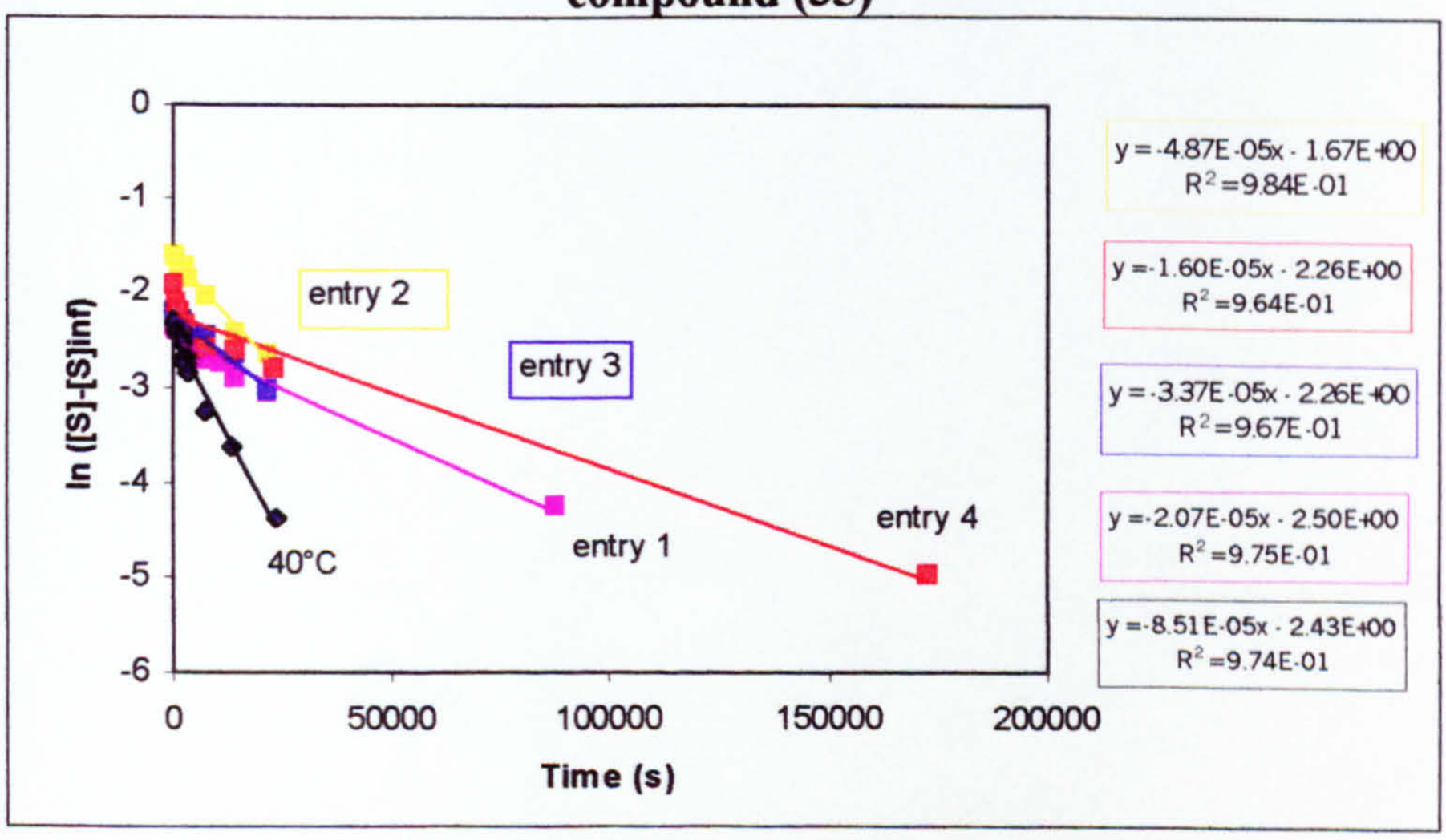


(35)

When the concentration of sulfide is doubled the rate of reaction is unaffected, meaning that the rate is independent of sulfide concentration (**Table 5.8**). Increasing the hydrogen peroxide concentration by 13 times causes the reaction rate to increase 5-fold. The rate of reaction is increased between 3-4 times when the mediator concentration is quadrupled, so the rate is apparently proportional to the concentration of the benzoxazolium salt.

The concentration-time data for all of the reactions (**Table 5.8**; entries 1-4) can be fitted to equation **[14]** with good correlation (R^2 = 0.964-0.984). The data collected at the higher temperature of 40°C, also showed a good fit to equation **[14]** (R^2 = 0.974). This supports the case that the mechanism of the oxidation involves a catalytic oxidation, whilst the concentration of mediator is slowly diminishing (**Scheme 5.3**).

Figure 5.4 Correlation of *ln* {[S] – [S]∞} with time for oxidations mediated by compound (35)



Increasing the initial concentration of hydrogen peroxide has the effect of doubling the conversion of sulfide after 24 hours to 66 % (**Table 5.9**, entry 4); there is no further oxidation over the next 24 hours. Increasing the concentration of mediator by four times increases the conversion from 33 to 71 % (entry 2).

Table 5.8 Initial rates of sulfide consumption and sulfoxide production mediated by compound (35)

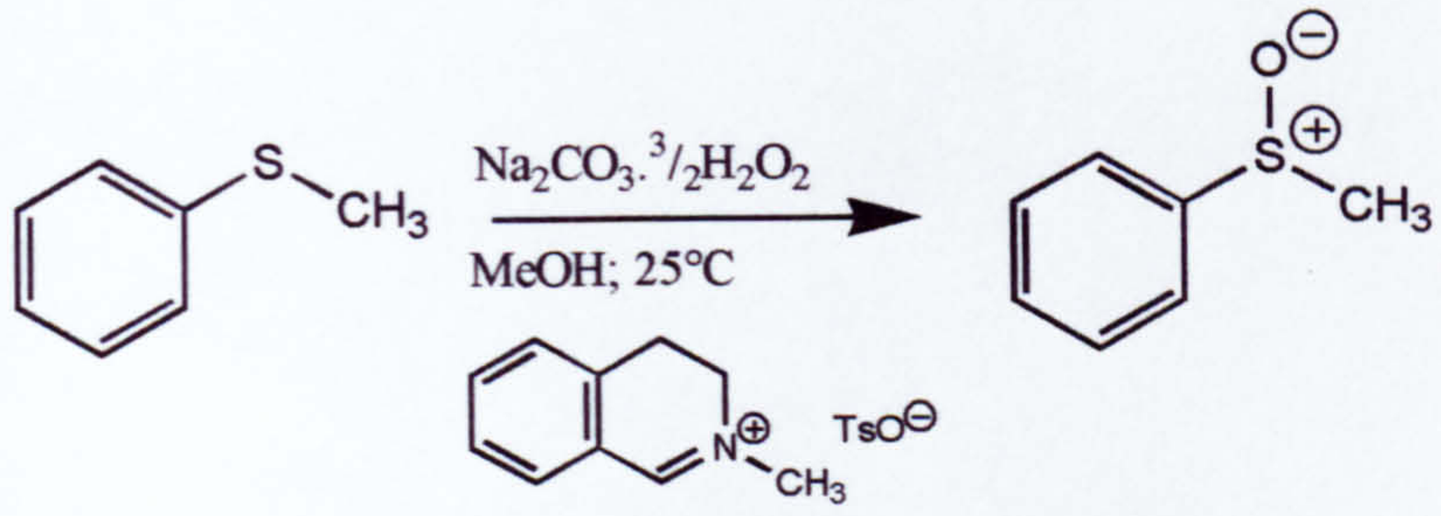
Entry	$[P]_0$[a] ($mmol.L^{-1}$)	$[S]_0$ ($mmol.L^{-1}$)	$[M]_0$ ($mmol.L^{-1}$)	-d[S]/dt ($mol.L^{-1}s^{-1}$)	R^2	Relative rate	d[SO]/dt ($mol.L^{-1}s^{-1}$)	R^2	Relative rate
1	17	268	68	$4.4x10^{-6}$	0.959	1.0	$6.4x10^{-6}$	0.999	1.0
2	17	268	272	$1.3x10^{-5}$	0.954	3.0	$1.7x10^{-5}$	0.988	2.7
3	17	537	67	$4.6x10^{-6}$	0.998	1.0	$4.2x10^{-6}$	0.999	0.7
4	220	268	67	$2.1x10^{-5}$	0.952	4.8	n.d.		

[a] Determined by titration; constant throughout reaction

Table 5.9 Conversion of sulfide mediated by compound (35)

Entry	Constant Concentration [P] ($mmol.L^{-1}$)	$[S]_0$ ($mmol.L^{-1}$)	$[M]_0$ ($mmol.L^{-1}$)	% Conversion To Sulfoxide	
				(24 hours)	(48 hours)
1	17	268	68	33	40
2	17	268	272	71	74
3	17	537	67	16	20
4	220	268	67	66	66

5.1.7 2-Methyl-3,4-dihydroisoquinolinium tosylate (54)

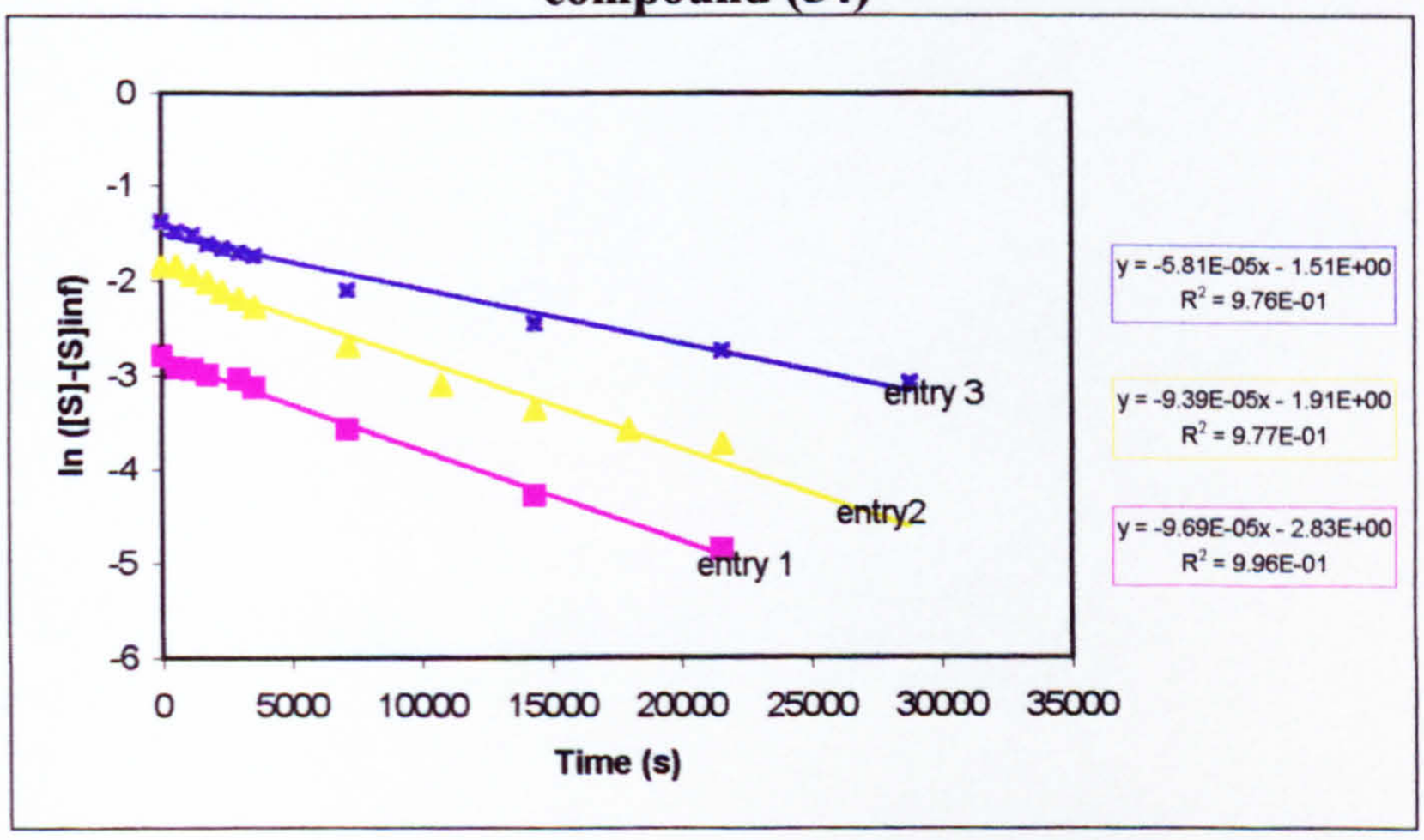


Scheme 5.7

From these results one can see that the rate of the reaction is proportional to the initial concentration of 2-methyl-3, 4-dihydroisoquinolinium tosylate (**Table 5.10**, entries 1 & 2) and is independent of the initial concentration of thioanisole (entries 2 & 3). This implies that the rate determining step is the initial formation of the oxygen transfer agent from the iminium salt and hydrogen peroxide and the subsequent oxidation of the sulfide is fast. Unfortunately, in this case, the rate of reaction with increased hydrogen peroxide was not measured because of time restrictions.

For all of the reactions (entries 1-3) the concentration-time data can be fitted to equation **[14]** with excellent correlation over the entire period of the reaction (R^2 = 0.976-0.996). This is consistent with the mechanism shown in **Scheme 5.3**.

Figure 5.5 Correlation of *ln* {[S] – [S]$_\infty$} with time for oxidations mediated by compound (54)



When eqimolar quantities of mediator and sulfide were employed, 76 % sulfoxide was produced after 24 hours (**Table 5.11**, entry 2).

Table 5.10 Initial rates of sulfide consumption and sulfoxide production mediated by compound (54)

Entry	$[P]_0$[a] ($mmol.L^{-1}$)	$[S]_0$ ($mmol.L^{-1}$)	$[M]_0$ ($mmol.L^{-1}$)	-d[S]/dt ($mol.L^{-1}s^{-1}$)	R^2	Relative rate	d[SO]/dt ($mol.L^{-1}s^{-1}$)	R^2	Relative rate
1	17	268	68	$5.2x10^{-6}$	0.990	1.0	$5.5x10^{-6}$	0.999	1.0
2	17	255	268	$2.2x10^{-5}$	0.995	4.2	$1.8x10^{-5}$	0.995	3.3
3	17	537	268	$1.9x10^{-5}$	0.986	3.9	$2.2x10^{-5}$	0.973	4.0

[a] Determined by titration; constant throughout reaction

Table 5.11 Conversion of sulfide mediated by compound (54)

Entry	Constant Concentration [P] ($mmol.L^{-1}$)	$[S]_0$ ($mmol.L^{-1}$)	$[M]_0$ ($mmol.L^{-1}$)	% Conversion To Sulfoxide (24 hours)	% Conversion To Sulfoxide (48 hours)
1	17	268	68	23	27
2	17	255	268	76	82
3	17	537	268	44	50

5.1.8 Conclusions

For all of the benzoxazolium salts, the rate of reaction appears to be proportional to the concentration of the mediator and independent of sulfide concentration. The effect of hydrogen peroxide concentration is not clear. In the case where equimolar quantities of 2-chloro-substituted benzoxazolium salt **(41)** and sulfide were employed, the sulfide is totally converted to sulfoxide after 24 hours. The 2-*tert*-butyl compound **(37)** also produces more sulfoxide than 2-methyl-3,4-dihydroisoquinolinium tosylate **(54)**, which is known to be active in hard surface cleaning applications.

In this series of benzoxazolium salts the rate of oxidation of thioanisole in the standard reaction was fastest for compound **(41)** (2-Cl), also in the reactions with 1: 1 (sulfide: mediator), followed by **(36)** (2-Ph) and then **(37)** (2-*t*-Bu). Compound **(35)** (2-H) was the slowest; the dihydroisoquinolinium salt **(54)** has a slightly faster rate than **(35)**. When increased hydrogen peroxide concentrations were used, the 2-chloro substituted compound **(41)** did not give the fastest rate of oxidation. The rate was the same as **(36)** (2-Ph) and slower than **(37)** (2-*t*-Bu) or **(35)** (2-H). Compound **(41)** also produces the least sulfoxide under these conditions and **(36)** the most; this indicates that the presence of high peroxide concentrations is deleterious to **(41)**. One possible explanation for this is that the active oxidant formed from **(41)** may be able to take part in the Radziszewski oxidation, although there is no direct evidence for this.

The correlation of *ln* $\{[S] - [S]_\infty\}$ with time, in accordance with **[14]**, for all of the benzoxazolium salts and 2-methyl-3,4-dihydroisoquinolinium tosylate **(54)** supports the mechanism proposed in **Scheme 5.3**. However, the attempted calculation of rate constants from the slopes and intercepts of the plots gives conflicting data. The use of the slopes of the plots (entries 1-3) to measure the apparent rate constant for the depletion of mediator agrees within experimental error between the different runs **(Table 5.12)**. However, the use of the intercept and slope to calculate the value of k_1 gives a wide spread of results.

As stated earlier the mechanism in **Scheme 5.3** cannot be distinguished from that shown in **Scheme 5.6**, or indeed from any similar mechanism where the mediator or an intermediate formed from it is slowly depleted. In reality, the loss of mediator that occurs is probably a combination of the loss of the mediator and the loss of the intermediate. Therefore, the measured rate constant, calculated from the gradient of the plot, represents the total loss of mediator by all processes. The values

were calculated using the data from entries 1-3, because the observed rate constant will include contributions from hydrogen peroxide and base concentration, meaning that the constants calculated for entry 4 will deviate from the rest.

Table 5.12 Values of k_{obs} for the heterogeneous oxidations

Compound	k_{obs} (s^{-1} x10^{-5})[a]	R^2	k_{obs} (s^{-1} x10^{-5})[b]	R^2
(35)	3.4	0.967	8.5	0.974
(36)	2.6	0.962	14	0.998
(37)	2.7	0.967	6.4	0.923
(41)	6.9	0.960	n.a.	-
(54)	8.3	0.976	n.d.	-

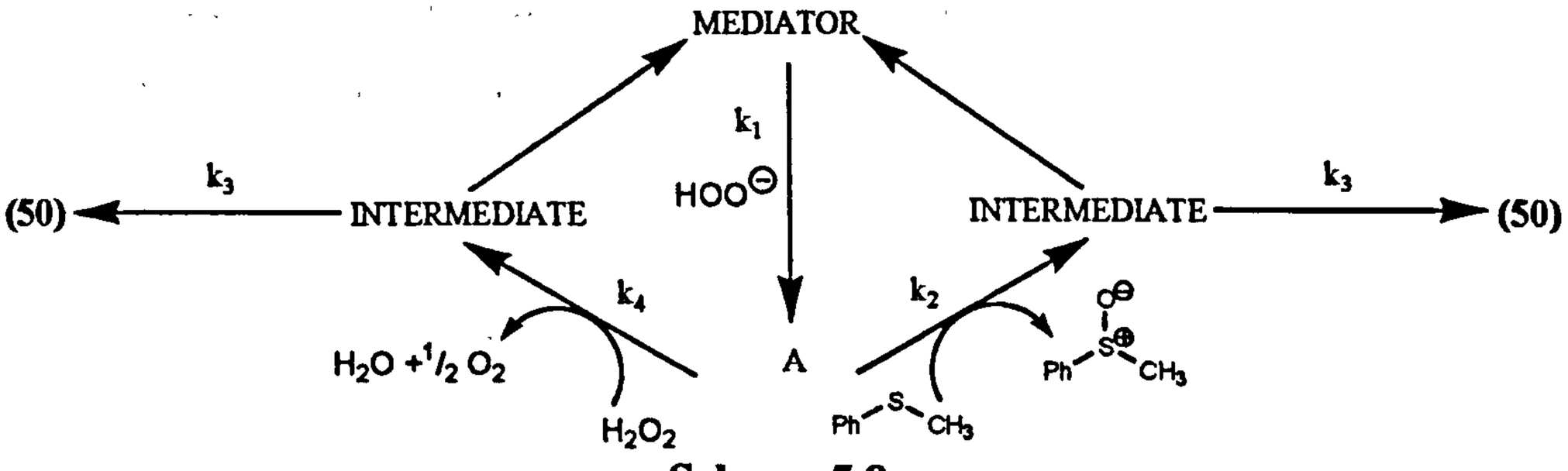
[a] 25°C; average of three runs
[b] 40°C.

One can see that in all cases the observed rate constant for the loss of the mediator increases with temperature, as is expected. For the 2-phenyl substituted benzoxazolium salt **(36)** the loss of mediator is significantly faster at 40°C, explaining why the observed loss of sulfide is apparently slower for this compound.

Reinvestigation of the proposed reaction mechanism and the assumptions made in interpreting the rate data reveals that the true rate of reaction is better described by **[18]**. For example, the additional terms in the integrated rate equation become significant if the decomposition of the mediator or an intermediate involves reaction with hydrogen peroxide.

$$-\delta[S]/\delta t = \{k_2 [S]\, k_1 [M]\, [P]\} / \{ k_4 [P] + k_2 [S]\} \qquad \textbf{[18]}$$

For entries 1-3 **(Tables 5.1- 5.11)** the concentration of hydrogen peroxide is low (k_4 [P] is small) and so **[14]** is obeyed. However, for the reactions with increased hydrogen peroxide concentration, the significance of the denominator is increased. This interpretation also accounts for the apparent independence of the rate from hydrogen peroxide concentration. This observation could be confirmed by carrying out additional experiments, in the presence of high hydrogen peroxide concentrations and observing the dependence of the rate upon sulfide concentration.



Scheme 5.8

The initial rate measurement might not reveal the true rate law in a complex reaction, for example if any of the products are involved in intermediate reaction steps.[3] In these oxidations, the hydrogen peroxide used will produce water, which may affect the rate in several ways. For example, the rate of decomposition of the mediator may be dependent upon the concentration of water, or the rate of other processes could also be affected. That the reaction occurs by a complex mechanism is indicated by the fact that the rate of oxidation does not increase with temperature for the 2-phenyl substituted benzoxazolium salt **(36)**.

5.2 Competitive oxidation of substituted thioanisoles

5.2.1 Introduction to structure-activity relationships

Reaction rates and equilibrium constants are both related to free energy changes, so these empirical properties can be described in terms of parameters describing molecular structure (σ). In 1933 Hammett derived a linear free energy relationship between the electronic properties of carboxylic acids and their equilibrium constants and the reactivity of their derivatives. He discovered that the observed rates of aminolysis of substituted aromatic esters were directly proportional to the ionization constants of corresponding acids.

Derivation of the Hammett equation:

$$\log k = \rho \log K + c$$

$$\log (k_X/k_H) = \rho \log (K_X/K_H)$$

$$\log (k_X/k_H) = \sigma\rho \qquad \textbf{[19]}$$

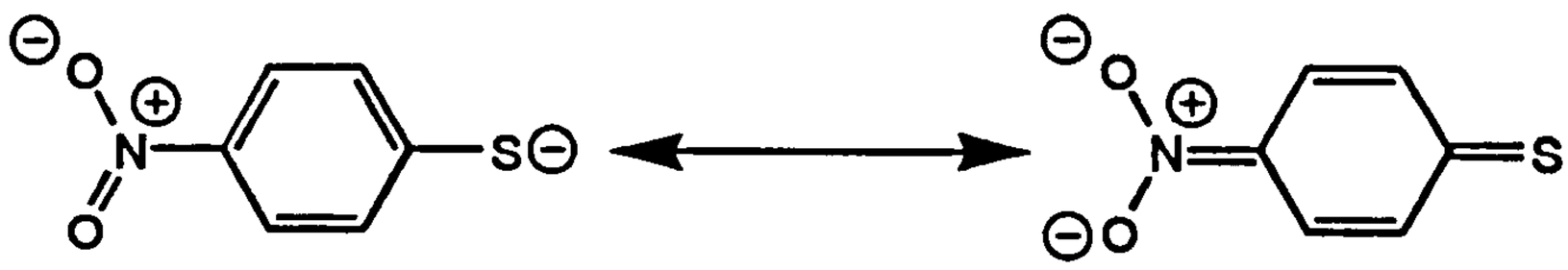
The σ value is derived from a standard reference reaction and represents a combination of the total electrical effects (resonance plus field effects) of the substituent. The magnitude of σ represents an empirical measure of the strength of the electron-withdrawing or donating properties of the substituent. Electron-withdrawing substituents have positive σ values and electron-donating substituents have negative σ values.

In some situations the σ constant for certain substituents does not give good correlation, so special substituent constants have been defined. In reactions where the substituent can conjugate directly with electron rich reaction centres (e.g. *p*-nitro group), σ^- is used; σ^+ values are used when a substituent (e.g. OMe) can conjugate to an electronically deficient reaction site.

The reaction constant ρ measures the susceptibility of a particular reaction to electrical effects. It relates the effect of substituents on that reaction to the effect of those substituents on the standard benzoic acid equilibrium. ρ, for rate processes, can be calculated from the slope of a plot of $\log (k_X/k_H)$ against σ (see equation **[19]**) and is dependent on reaction mechanism.

5.2.2 Choice of substituent constant

As mentioned above, it has been discovered that in cases where the substituent can interact directly with the reaction centre, alternative substituent constants must be used. For example, when correlating the acidity constants of substituted thiophenols,[4, 5] special σ values (denoted σ^-) were necessary for the *p*-NO_2 group because it can conjugate directly with the developing negative charge at the reaction centre (**Scheme 5.9**). In this case a σ value of 1.00 is given; this is larger than the value given by Hammett for benzoic acids (0.778), but smaller than the σ value calculated for anilinium ions (1.27), which has been more commonly used.[6]



Scheme 5.9

In certain electrophilic reactions (e.g. solvolysis of benzyl tosylates), it is also necessary to use alternative σ values for substituents that can interact with the transition state by resonance stabilisation (e.g. *p*-OMe).[7, 8] Such situations require a substituent constant (denoted σ^+) that is more negative than the standard Hammett value (-0.764 against –0.268).

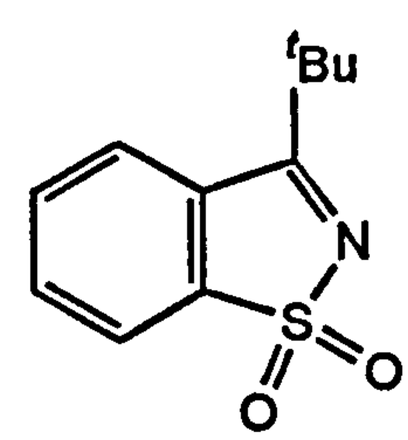
Scheme 5.10

In order to further investigate the mechanism of the *O*-transfer reactions, the effect upon the rate of placing substituents in the aromatic ring of thioanisole was examined. It should be noted here that although the measured rate of reaction is independent of sulfide concentration, the use of competition experiments allows the relative reactivities of *p*-substituted and unsubstituted sulfides to be assessed.

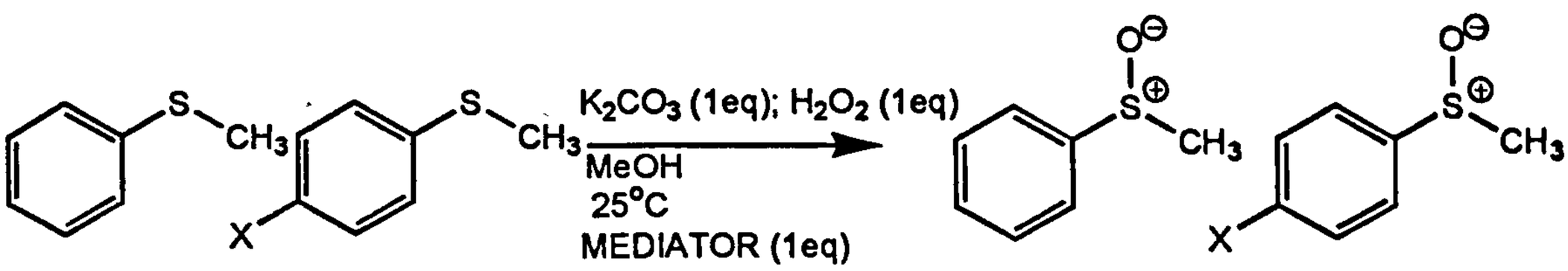
5.2.3 Assessment of substituent effects

Some of the 2-substituted benzoxazolium salts were used as mediators of oxygen transfer in a set of competitive oxidations of thioanisole and 4-substituted thioanisoles (**Scheme 5.11**). In this set of reactions, one equivalent of mediator was

used (to make the reaction proceed at a reasonable rate) and one equivalent of aqueous hydrogen peroxide was used so that the sulfides would never be completely converted to sulfoxides; this also ensured that the reactions were homogeneous. 3-*tert*-Butyl-1,2-benzisothiazole 1,1-dioxide **(65)** was also assessed as a mediator of the sulfoxidation under this set of reaction conditions.



(65)



Scheme 5.11

Aliquots were taken from the reaction mixture at appropriate time intervals and analysed using reversed-phase HPLC (using biphenyl as an internal standard). The concentrations of the substituted and unsubstituted sulfides were plotted against time and the relative rates of reaction (k_X/k_H) were calculated using equation **[20]** (for derivation see chapter 7). Since this equation takes into account more data points it should give a more accurate representation of the relative rates than initial rate measurements. These values were plotted against the various Hammett σ values[6] in order to find the best correlation. The conversion of the *p*-substituted thioanisoles after 24 hours by each mediator are also shown in the following tables.

$$k_X/k_H = ln\,([S_X]/[S_X]_0)/\ ln\,([S_H]/[S_H]_0) \qquad [20]$$

Where: k_X = rate of oxidation of substituted thioanisole;
k_H = rate of oxidation of thioanisole;
$[S_X]$ = concentration of substituted thioanisole;
$[S_H]$ = concentration of thioanisole.

5.2.4 Uncatalysed reactions

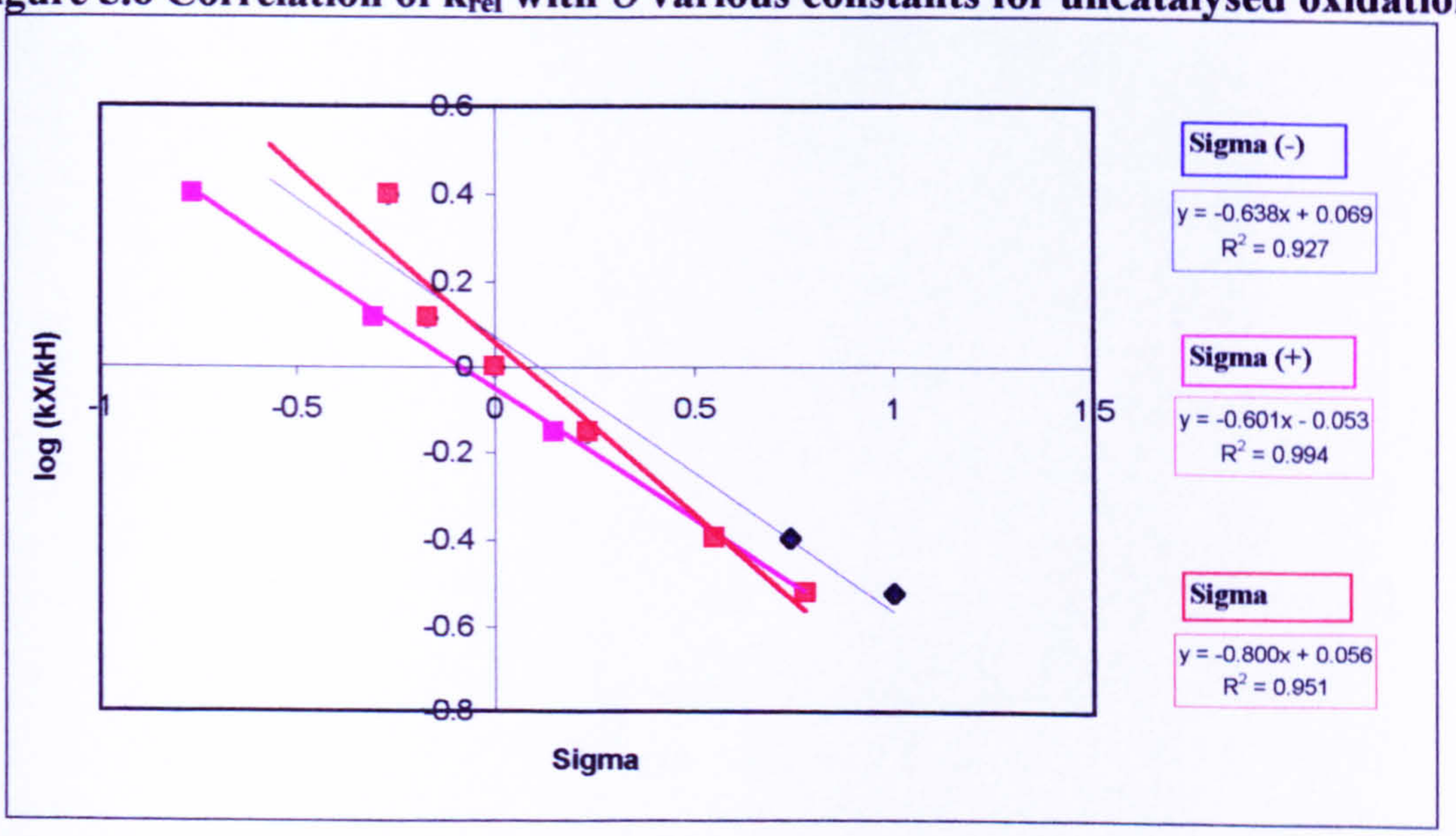
In order to confirm that the uncatalysed oxidation of the *p*-substituted sulfides did not proceed appreciably, the oxidations were carried out in the absence of any mediator. The % loss of each sulfide after 48 hours is shown in **Table 5.13**.

Table 5.13 % Conversion of sulfide in uncatalysed oxidations

X	% Conversion
OMe	4.8
CH_3	2.4
H	1.9
Br	1.3
CF_3	0.7
NO_2	<0.5

These values can also be analysed using the Hammett structure activity relationship; the values correlate better with σ^+ ($R^2 = 0.994$) rather than σ ($R^2 = 0.951$) or σ^- ($R^2 = 0.927$). The ρ value obtained is rather low (-0.60), which indicates that the reaction is not very susceptible to substituent effects (**Figure 5.6**).

Figure 5.6 Correlation of k_{rel} with σ various constants for uncatalysed oxidation



5.2.5 3-Methylbenzoxazolium tetrafluoroborate (35)

Table 5.14 Conversion of sulfides after 24 hours

X	% Conversion of thioanisole	% Conversion of *p*-substituted thioanisole
OMe	25	50
CH_3	19	29
Br	24	14
CF_3	23	7
NO_2	18	4

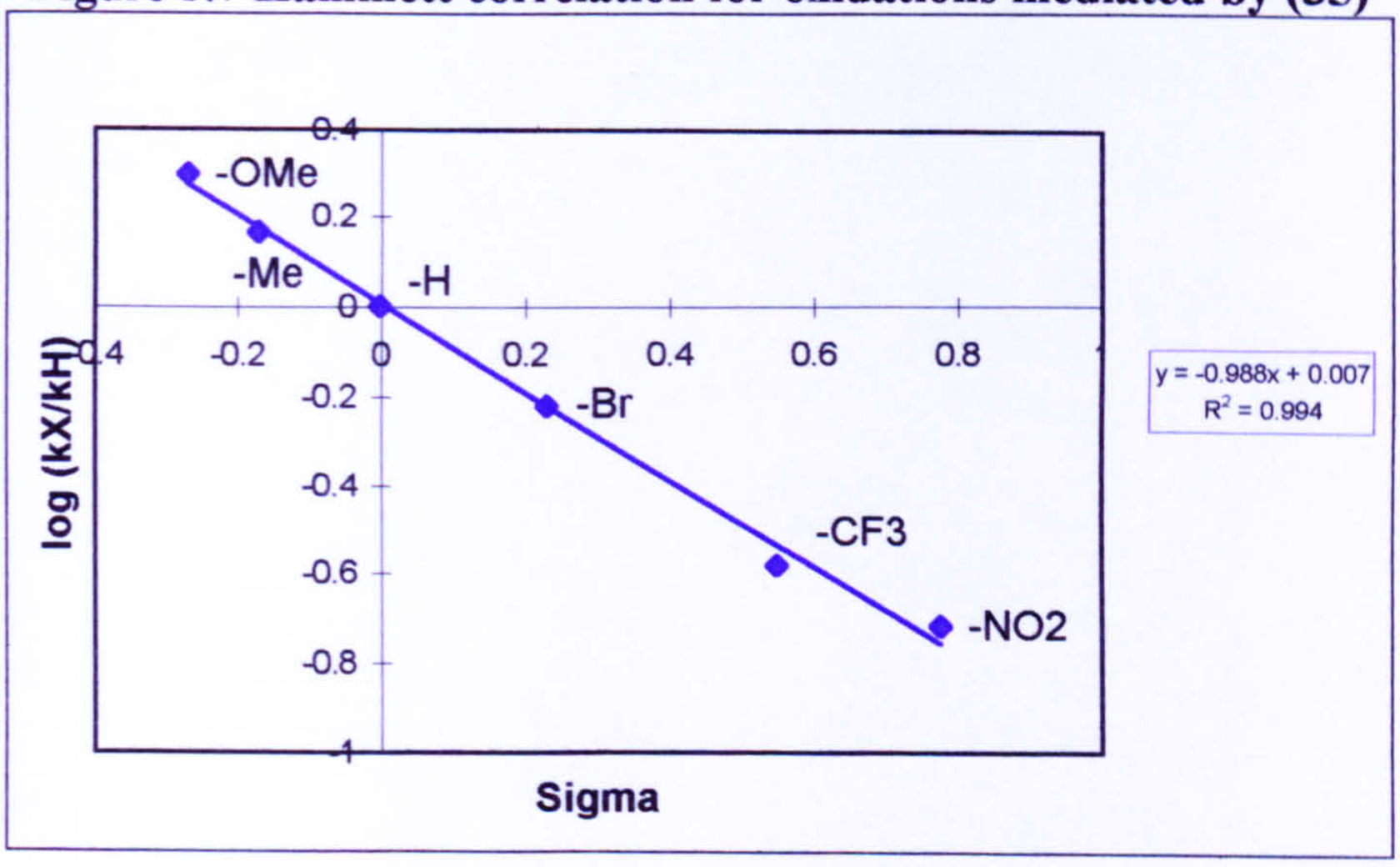
$[S_X]_0 = [S_H]_0 = [M]_0 = [P]_0 = 57.9$ mM

Table 5.15 Relative rates of reactivity for substituted thioanisoles

X	σ	k_X/k_H	$\log(k_X/k_H)$
OMe	-0.268	2.0	0.297
CH_3	-0.17	1.5	0.176
H	0	1	0
Br	0.232	0.60	-0.222
CF_3	0.551	0.26	-0.585
NO_2	0.778	0.19	-0.721

An excellent fit is obtained for a plot of σ against the relative rates of reaction ($R^2 = 0.994$); the value of ρ is -0.99. The correlation of the data with σ^- and σ^+ is not significant ($R^2 = 0.950$ in both cases).

Figure 5.7 Hammett correlation for oxidations mediated by (35)



5.2.6 2-Chloro-3-ethylbenzoxazolium tetrafluoroborate (41)

Table 5.16 Conversion of sulfides after 24 hours

X	% Conversion of thioanisole	% Conversion of *p*-substituted thioanisole
OMe	19	40
CH_3	11	24
CF_3	35	8
NO_2	17[a]	4[a]

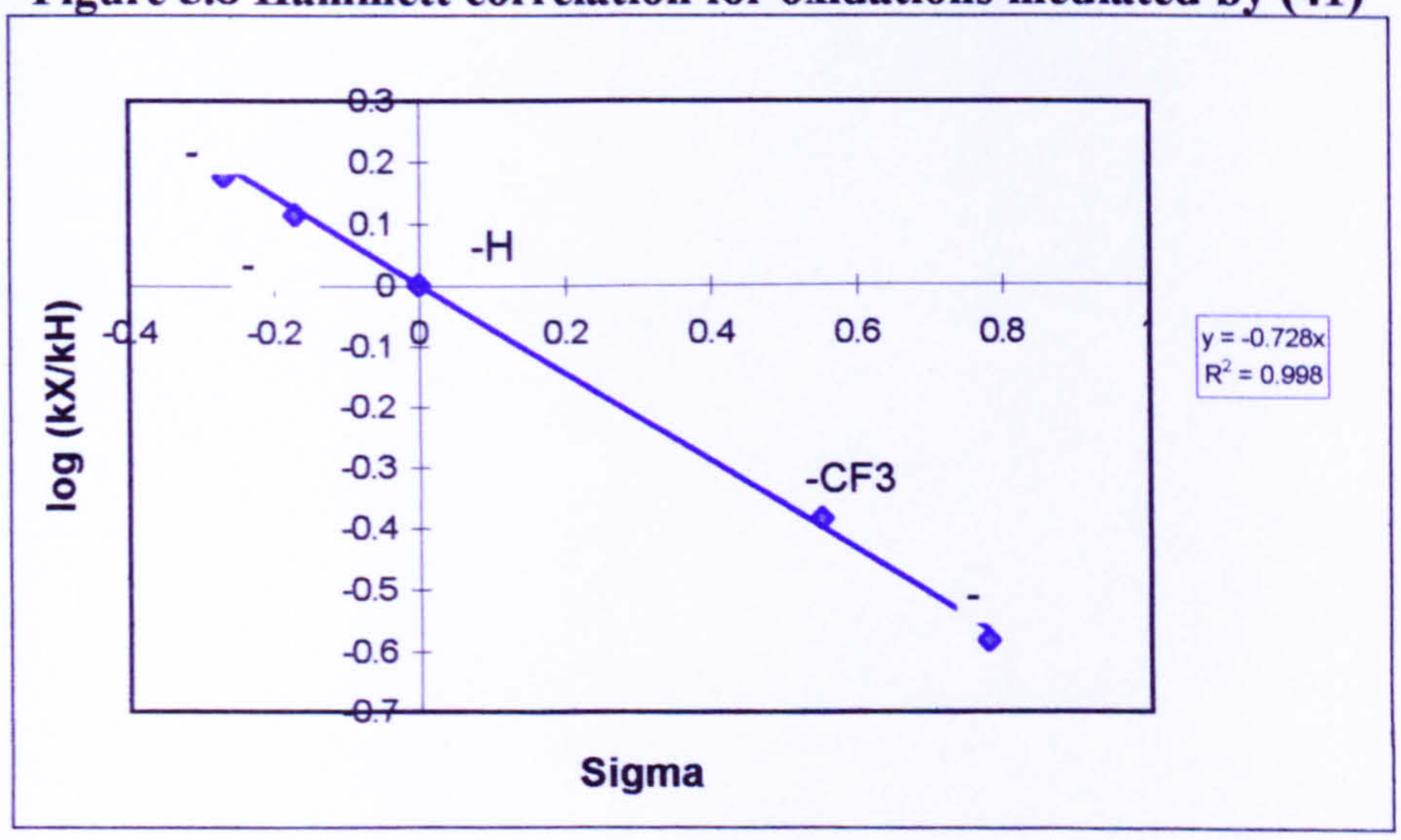
[a] 315 mins, no further conversion observed

Table 5.17 Relative rates of reactivity for substituted thioanisoles

X	σ	k_X/k_H	$\log(k_X/k_H)$
OMe	-0.268	1.5	0.176
CH_3	-0.17	1.3	0.114
H	0	1	0
CF_3	0.551	0.41	-0.387
NO_2	0.778	0.26	-0.585

Application of the Hammett equation to the relative rate values produces an excellent correlation ($R^2 = 0.998$) with σ, giving a ρ value of -0.73. The correlation for σ^+ is not significant ($R^2 = 0.924$), although a good fit is obtained for σ^- ($R^2 = 0.993$), indicating that conjugation from the nitro group may play a small part in the mechanism ($\rho^- = -0.50$).

Figure 5.8 Hammett correlation for oxidations mediated by (41)



5.2.7 2-Phenyl-3-methylbenzoxazolium tetrafluoroborate (36)

Table 5.18 Conversion of sulfides after 24 hours

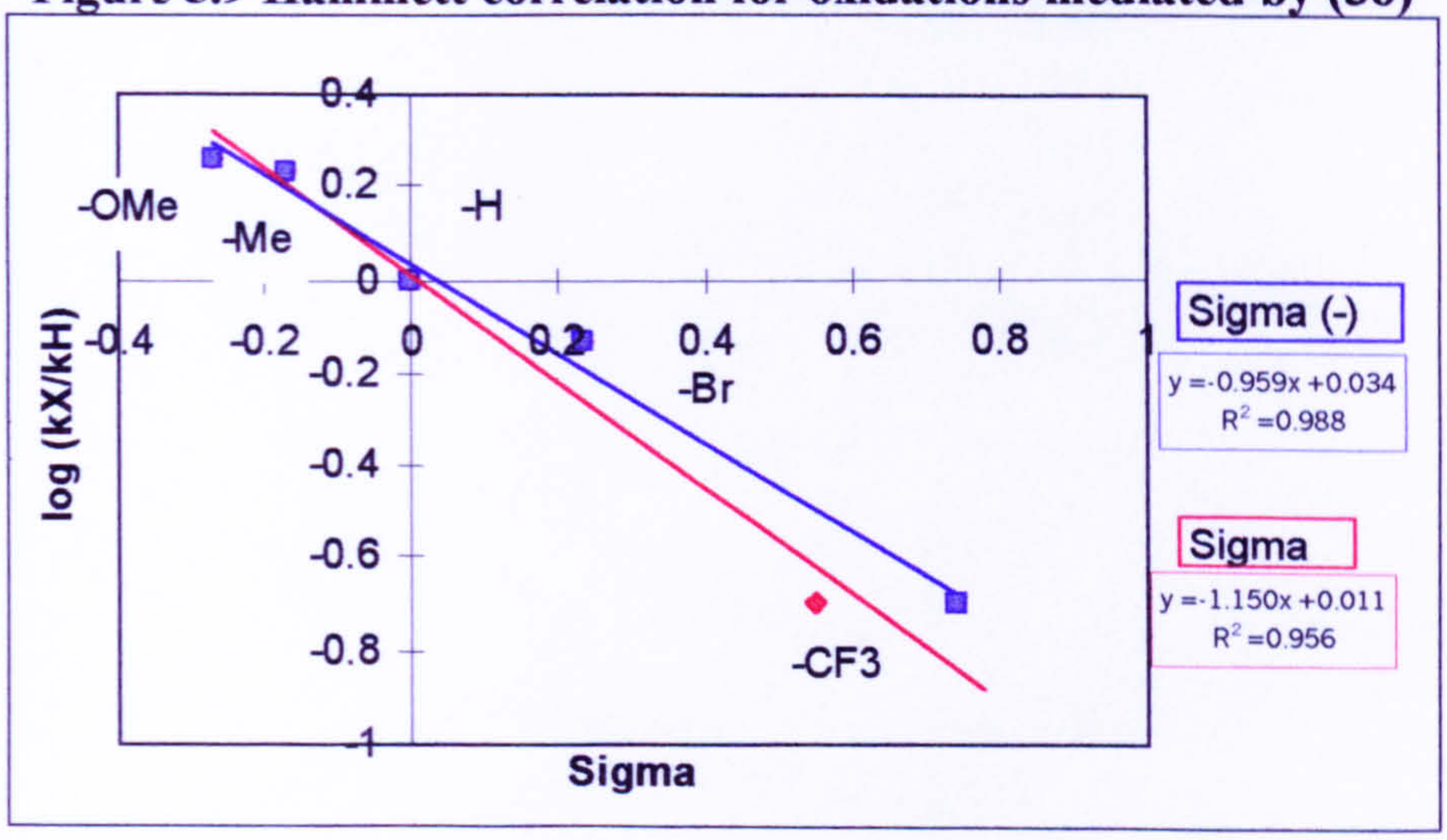
X	% Conversion of thioanisole	% Conversion of *p*-substituted thioanisole
OMe	15	31
CH_3	15	21
Br	15	8
CF_3	23	4

Table 5.19 Relative rates of reactivity for substituted thioanisoles

X	σ	k_X/k_H	$\log(k_X/k_H)$
OMe	-0.268	1.8	0.255
CH_3	-0.17	1.2	0.230
H	0	1	0
Br	0.232	0.74	-0.131
CF_3	0.551	0.20	-0.699

For compound **(36)** the relative rate data is better correlated with σ^- ($R^2 = 0.988$) than σ ($R^2 = 0.956$); this suggests that in this case conjugation is important, particularly conjugation between sulfur and electron withdrawing groups. The values obtained for ρ and ρ^- are -1.2 and -0.96 respectively.

Figure 5.9 Hammett correlation for oxidations mediated by (36)



5.2.8 2-*t*-Butyl-3-methylbenzoxazolium tetrafluoroborate (37)

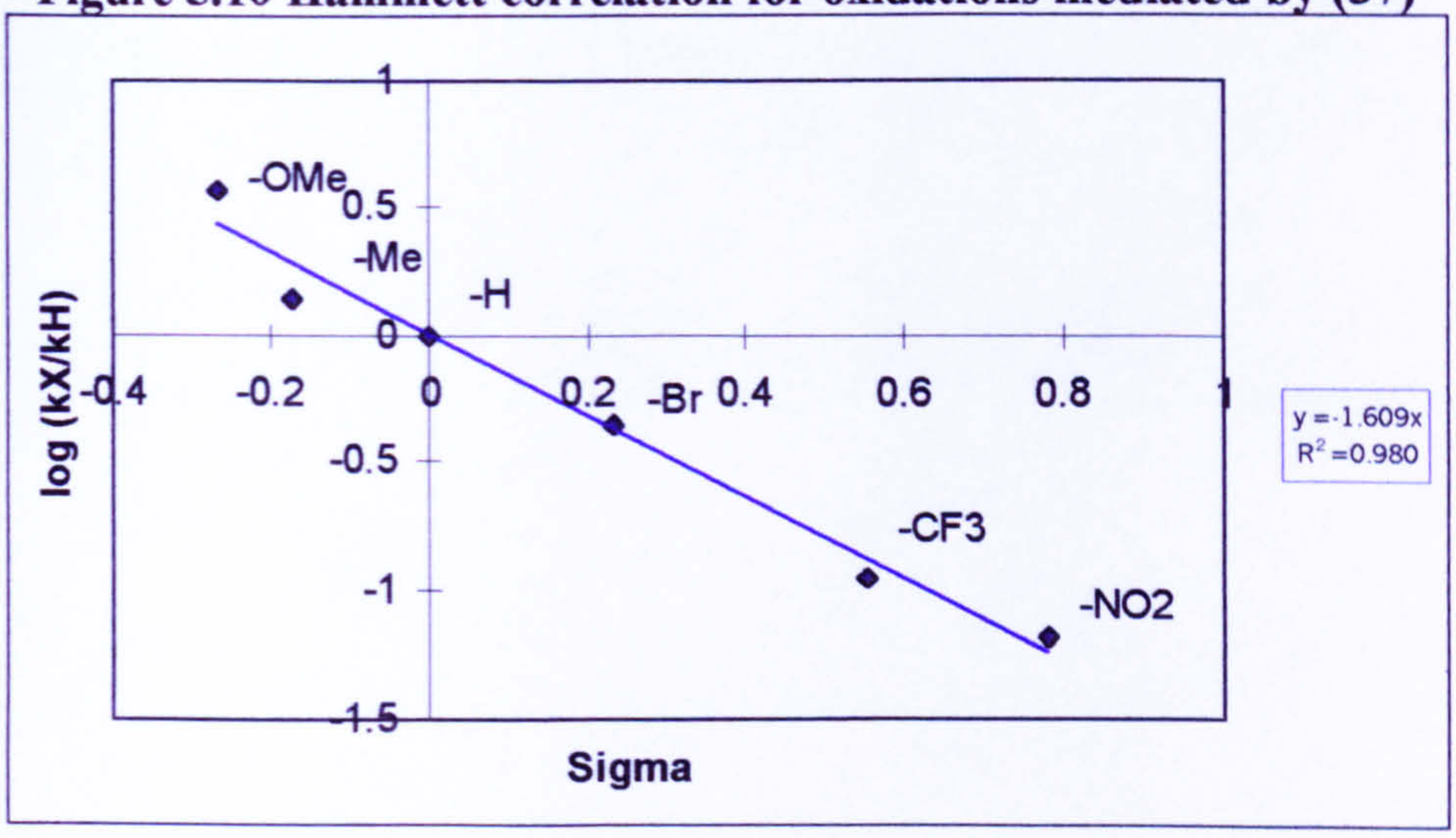
Table 5.20 Conversion of sulfides after 24 hours

X	% Conversion of thioanisole	% Conversion of *p*-substituted thioanisole
OMe	29	58
CH_3	37	50
Br	38	22
CF_3	46	8
NO_2	43	5

Table 5.21 Relative rates of reactivity for substituted thioanisoles

X	σ	k_X/k_H	$\log(k_X/k_H)$
OMe	-0.268	3.7	0.568
CH_3	-0.17	1.4	0.146
H	0	1	0
Br	0.232	0.44	-0.357
CF_3	0.551	0.11	-0.959
NO_2	0.778	0.065	-1.19

Figure 5.10 Hammett correlation for oxidations mediated by (37)



The best correlation is produced ($R^2 = 0.980$) when the relative rates are plotted against σ. The fits are not improved if σ^+ or σ^- values are used instead ($R^2 =$ 0.968 or 0.936); a ρ value of -1.6 is obtained for this mediator.

5.2.9 3-*tert*-Butyl-1,2-benzisothiazole 1,1-dioxide (65)

Table 5.22 Conversion of sulfides after 24 hours

X	% Conversion of thioanisole	% Conversion of *p*-substituted thioanisole
OMe	29[a]	66[a]
Br	61	37
CF_3	56	10
NO_2	16[b]	3[b]

[a] 362 mins

[b] 1140 mins; based on sulfoxide production

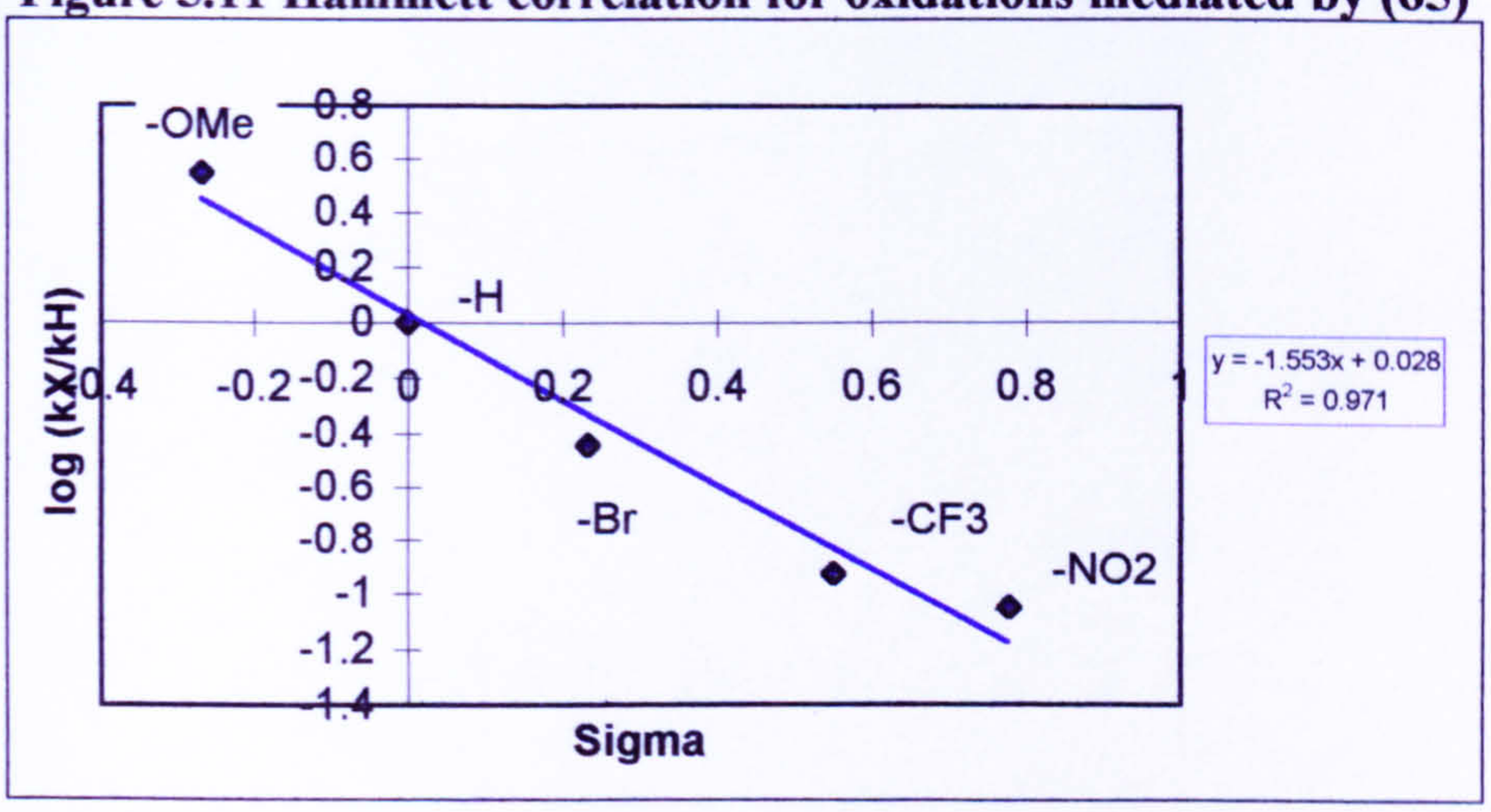
Table 5.23 Relative rates of reactivity for substituted thioanisoles

X	σ	k_X/k_H	$\log(k_X/k_H)$
OMe	-0.268	3.5	0.544
H	0	1	0
Br	0.232	0.36	-0.444
CF_3	0.551	0.12	-0.922
NO_2	0.778	0.09[a]	-1.05

[a] based on sulfoxide production

When the relative rate data is treated with Hammett's equation the best correlation is obtained using the standard σ values ($R^2 = 0.971$), producing a ρ value of -1.6. For σ^+ and σ^- the R^2 values are 0.961 and 0.884 respectively.

Figure 5.11 Hammett correlation for oxidations mediated by (65)



5.2.10 Conclusions

The fact that the relative reactivities are better correlated with Hammett σ values rather than σ^+ / σ^- in most cases justifies the choice of substituent constant. This also means that resonance between the substituents and reaction centre is not important in these reactions. Furthermore, it indicates that for the oxidation of a set of sulfides by a particular mediator, a common mechanism occurs for each sulfide. A change in the reaction mechanism or active oxidant would be indicated by a non-linear plot.

Correlation of relative rate data with σ^+ or σ^- as opposed to σ has been used to decide reaction mechanisms e.g. a correlation with σ^+ is taken as evidence of a single electron transfer mechanism in oxidations of alkyl aryl sulfides by

oxochromium (V) ion[9] or cytochrome P-450.[10] However, others have warned against settling on a reaction mechanism on this basis.[11, 12]

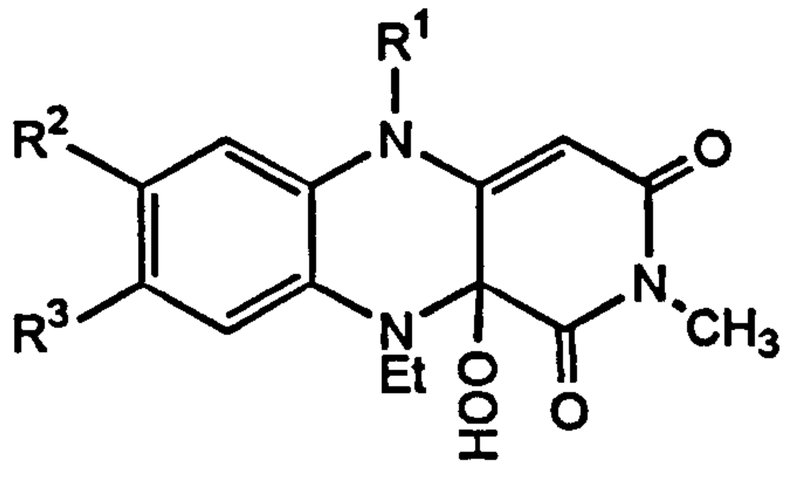
Table 5.24 Correlation between relative rates of oxidation and σ

Compound	ρ	R^2
(35)	-0.99	0.994
(41)	-0.73	0.998
(36)	-1.2	0.956
(37)	-1.6	0.980
(65)	-1.6	0.971

All of the Hammett plots had a negative slope, meaning that the rate of reaction is increased by the presence of electron donating groups and is decreased by electron withdrawing groups. This indicates that the dominant interaction in the reaction mechanism involves the transfer of electron density from the sulfide to the mediator. This is consistent with nucleophilic attack by the sulfide at the oxygen atom of an intermediate formed from hydrogen peroxide and the mediator.

2-*t*-Butyl-3-methylbenzoxazolium tetrafluoroborate **(37)** gives rise to the largest ρ value observed for the benzoxazolium mediators (-1.6), implying that the *O*-transfer agent derived from this compound is the most selective studied. This value is the same as that obtained for 3-*tert*-butyl-1,2-benzisothiazole 1,1-dioxide **(65)**. In this case there is other evidence supporting an α-hydroperoxyamine as the active oxidant.[13] A value of -1.7 has been calculated for the oxidation of *p*-substituted thioanisoles by isoalloxazine 4a-hydroperoxides **(67)**, [11] supporting the proposal that an α-hydroperoxyamine is the active oxidant in this case.

2-Phenyl-3-methylbenzoxazolium tetrafluoroborate **(36)** is less selective than **(37)**, having a ρ value of -1.2. These values are consistent with the fact that compounds **(37)** and **(36)** have the most sterically demanding substituents e.g. 2-*t*-butyl and 2-phenyl groups and so are expected to be the most selective of the benzoxazolium salts studied.



(67)

The least selective of the 2-alkyl/ aryl-benzoxazolium salts is the 2-*H*-substituted compound **(35)**, which has a ρ value of -0.99. This value is almost the same as that obtained in the oxidation of *p*-substituted thioanisoles by acetonitrile[14] and hydrogen peroxide (ρ = -1.0) where the active oxidant is proposed to be a peroxyimidic acid. However, for the acetonitrile/ hydrogen peroxide system, over-oxidation to sulfone was observed, meaning that the oxidant derived from 3-methylbenzoxazolium tetrafluoroborate **(35)** is more selective towards the oxidation of sulfoxides than the peroxyimidic acid.

2-Chloro-3-ethylbenzoxazolium tetrafluoroborate has the lowest ρ value observed in this series (-0.73), indicating that this compound is the least selective of the mediators tested. The value is very similar (-0.77) to that obtained for the oxidation of *p*-substituted thioanisoles by dimethyl dioxirane,[15] which is known to be a very powerful electrophilic oxidising agent.

A ρ value of -2.37 has been assigned to oxidations of substituted phenyl methyl sulfides by *N*-bromoacetamide in the presence of Hg (II).[16] The rate-determining step involves reaction of the sulfide with an electrophile to form a sulfonium ion. The fact that the benzoxazolium salts give a much lower ρ value means that the charge developing on *S* in the transitions state is much less and so the reaction is less influenced by substituents in the aromatic ring.

For all of the benzoxazolium salts, the total conversion of substituted and unsubstituted thioanisoles never reaches 100 %. Furthermore, hydrogen peroxide could be detected at the end of these reactions. This suggests that the mediator is consumed before full conversion of hydrogen peroxide can occur. Since there is hydrogen peroxide remaining at the end of the reaction, the mediator must be also destroyed by base. If the *o*-amidophenol was formed in the process of oxidation (of sulfide or hydrogen peroxide) then all of the hydrogen peroxide originally present would be used up. For the series of benzoxazolium salts, the most total conversion of sulfides is achieved by the *tert*-butyl salt **(37)**, followed by **(35)** (2-H). Compound **(41)** (2-Cl), which produces the most sulfoxide in the heterogeneous reactions, is only better than **(36)** (2-Ph) under these conditions, giving 40 % conversion. This can be accounted for by the high concentration of hydrogen peroxide in the homogeneous reactions accelerating the decomposition of this mediator, as was

observed in the heterogeneous reaction with high hydrogen peroxide concentration **(Table 5.7, entry 4)**.

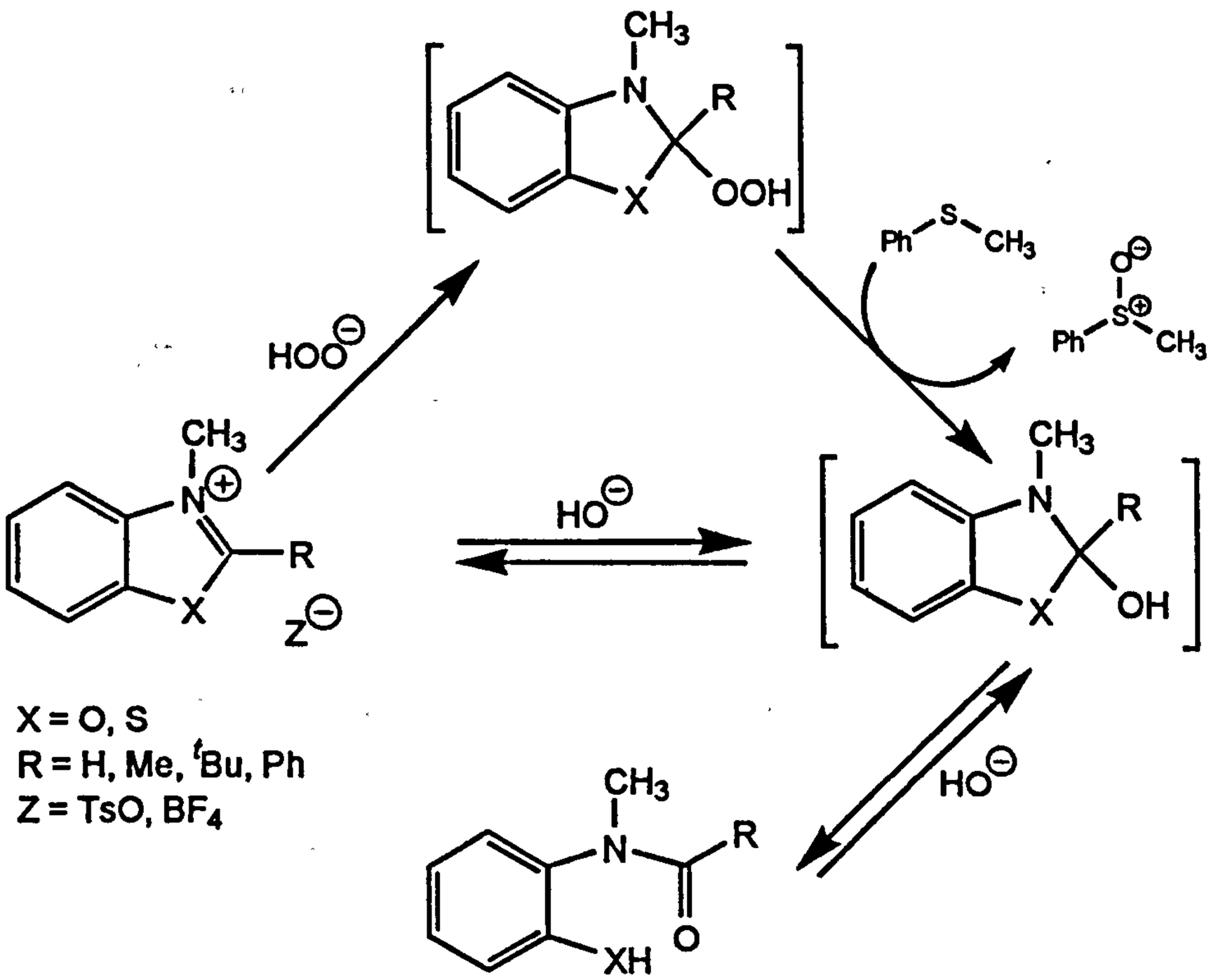
3-*tert*-Butyl-1,2-benzisothiazole 1,1-dioxide **(65)** gives a total conversion of almost 100 % for the more easily oxidized sulfides (X = OMe, Me), meaning that all of the hydrogen peroxide is used up in these cases. For the competitive oxidations of *p*-nitro and CF_3 substituted thioanisoles, the total conversion is lower. In addition, no hydrogen peroxide could be detected at the end of the oxidations; seemingly this is because the hydrogen peroxide is used up in another process, possibly the Radziszewski oxidation.

5.3 Mechanistic Interpretation

5.3.1 2-Alkyl- and 2-aryl-benzoxazolium salts

The data collected in the heterogeneous reactions leads to the conclusion that the reactions appear to be catalytic, but the catalysts are gradually decomposed in a separate process (**Scheme 5.12**). Reactions using *N*-(2-hydroxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide **(52)** as a mediator indicate that *o*-amidophenols are able to mediate the reaction, perhaps by reformation of the benzoxazolium salt.

This mechanism is also supported by the data obtained in the homogeneous reactions; firstly the sign of the ρ value indicates that the reaction mechanism involves transfer of electron density from the sulfide to the mediator. Secondly, the magnitude of ρ is in agreement with the proposal that an α-hydroperoxyamine is the active *O*-transfer agent.

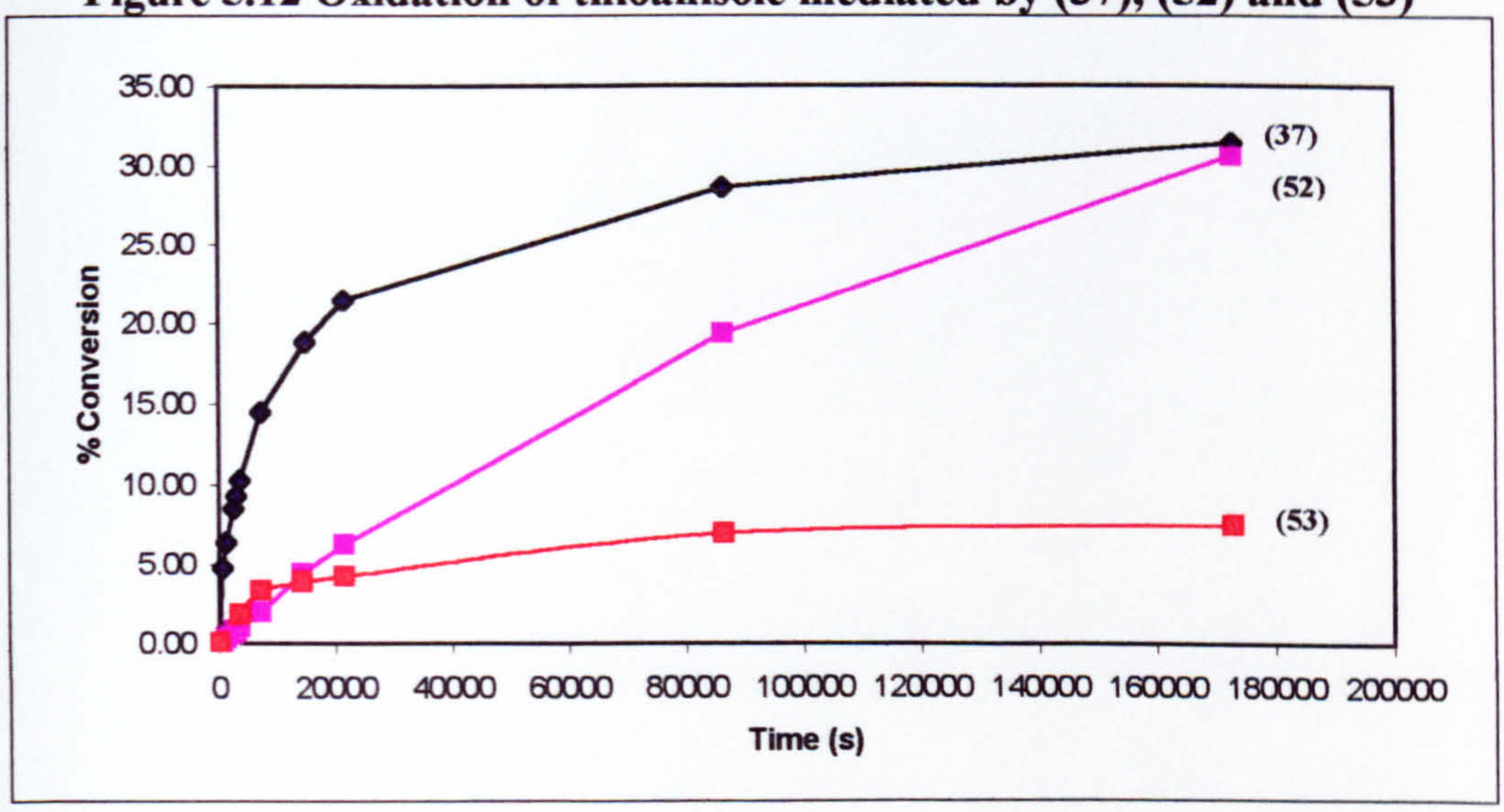


Scheme 5.12

Inspection of the concentration–time curves for 2-*t*-butyl-3-methylbenzoxazolium tetrafluoroborate **(37)** and the corresponding *o*-amidophenol **(52)** reveals that the salt **(37)** initially mediates the oxidation more rapidly than **(52)** (**Figure 5.12**). However, whilst the rate of oxidation falls off rather rapidly for the benzoxazolium salt, the rate appears to be constant over much of the reaction for the *o*-amidophenol. This result appears to be in conflict with the proposed mechanism

(Scheme 5.12), since if the benzoxazolium salts are converted to *o*-amidophenols under the reaction conditions, then the rate during the latter part of the oxidation mediated by the salt should be the same as that obtained for the *o*-amidophenol. However, the constant rate of oxidation by the *o*-amidophenol is clearly faster. This suggests that the benzoxazolium salts are present *'in situ'* as another unknown compound, which is converted to an *o*-amidophenol during the work up. The mechanism of oxidation mediated by the *o*-amidophenol **(52)** is unclear. *N*-(2-Methoxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide **(53)** gives only slightly more conversion than the uncatalysed reaction.

Figure 5.12 Oxidation of thioanisole mediated by (37), (52) and (53)

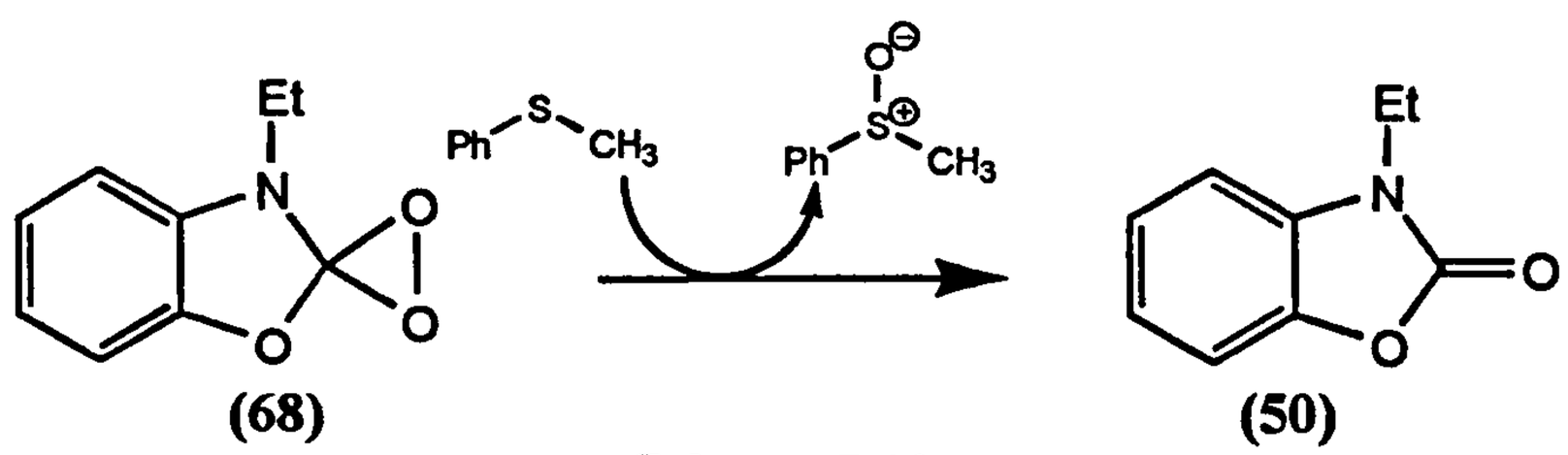


5.3.2 2-Chloro-3-ethylbenzoxazolium tetrafluoroborate (41)

The product of decomposition from 2-chloro-3-ethylbenzoxazolium tetrafluoroborate **(41)** does not mediate the oxidation of thioanisole. Thus any reformation of the benzoxazolium salt from **(50)** is not considered in this case and the catalytic cycle must be completed without the involvement of compound **(50)**. Possible active oxygen transfer agents that have been considered are the dioxirane **(68)**, the hydroperoxyiminium salt **(69)**, the α-hydroperoxyamine **(71)**, and the oxaziridinium salt **(73)**.

The low turnover in the presence of high hydrogen peroxide concentration suggests that the active oxidant or mediator is destroyed under such conditions and so the loss of mediator is thought to involve hydrogen peroxide in this case.

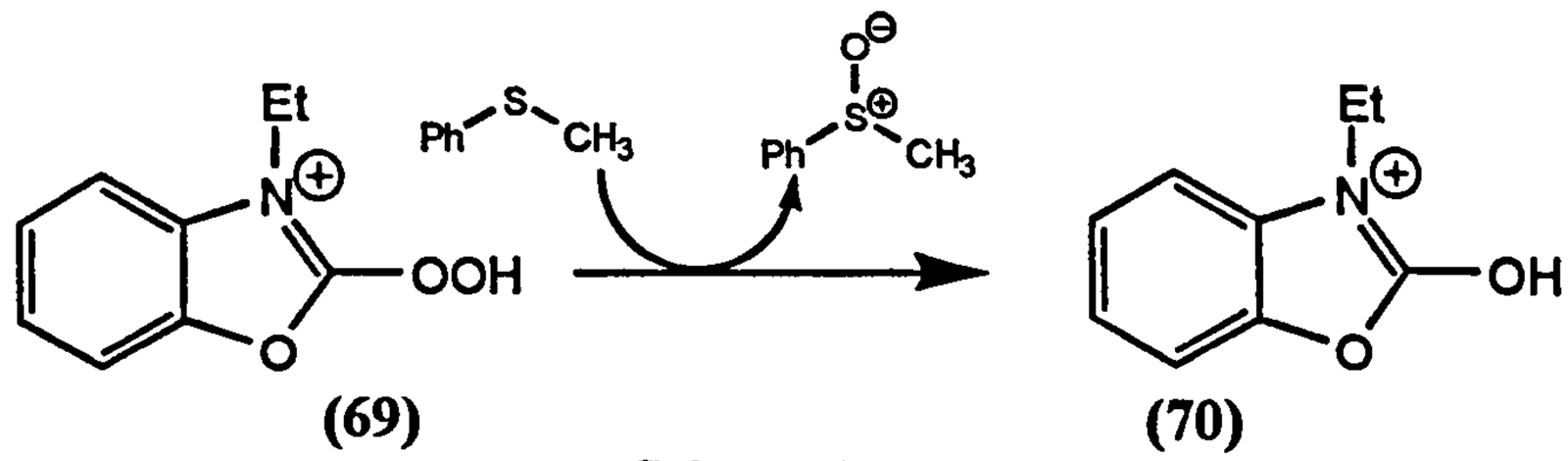
The three species that seem unlikely to form a catalytic cycle are compounds **(68)**, **(69)** and **(71)**, since their structure indicates that they are likely to be stoichiometric oxidants. After *O*-transfer the dioxirane **(68)** would form compound **(50)**, which is known not to mediate oxygen transfer (**Scheme 5.13**).



(68) **(50)**

Scheme 5.13

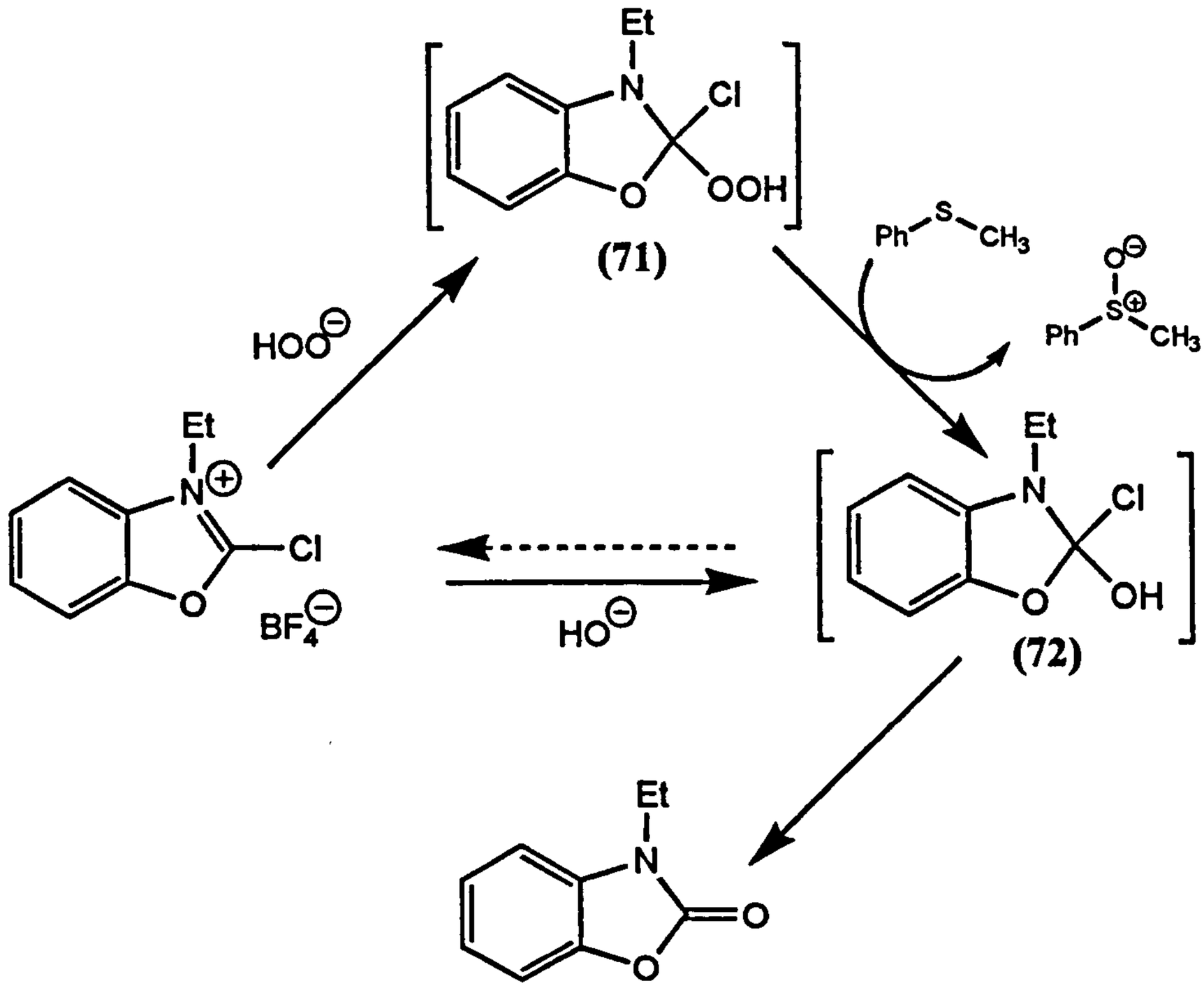
Oxygen transfer from **(69)** yields compound **(70)**, which is the protonated form of **(50)**. In order for a catalytic cycle to be reformed, nucleophilic addition by hydroperoxide anion would have to occur at a faster rate than deprotonation, which seems unlikely. Furthermore, the structurally similar hydroperoxy iminium salt **(46)**, formed from the Vilsmeier reagent and hydrogen peroxide, is a stoichiometric oxidant.



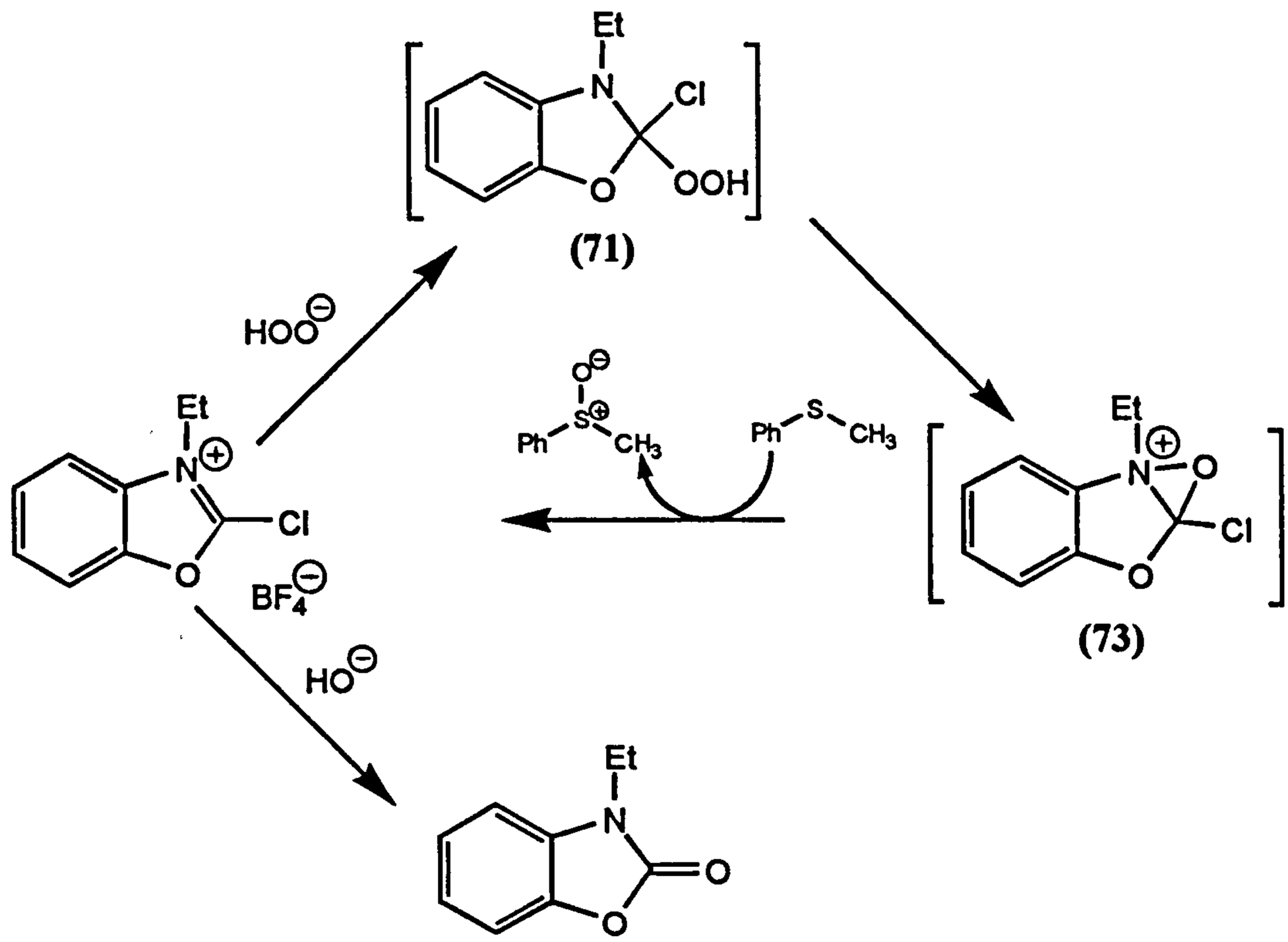
(69) **(70)**

Scheme 5.14

In order for the α-hydroperoxyamine **(71)** to participate in a catalytic cycle as the active oxidant, **(72)** must lose hydroxide ion rather than chloride to reform the benzoxazolium salt, which seems doubtful (**Scheme 5.15**). Alternatively, compound **(71)** can be converted to an oxaziridinium salt, which is transformed to the benzoxazolium salt after oxygen transfer to the sulfide (**Scheme 5.16**).



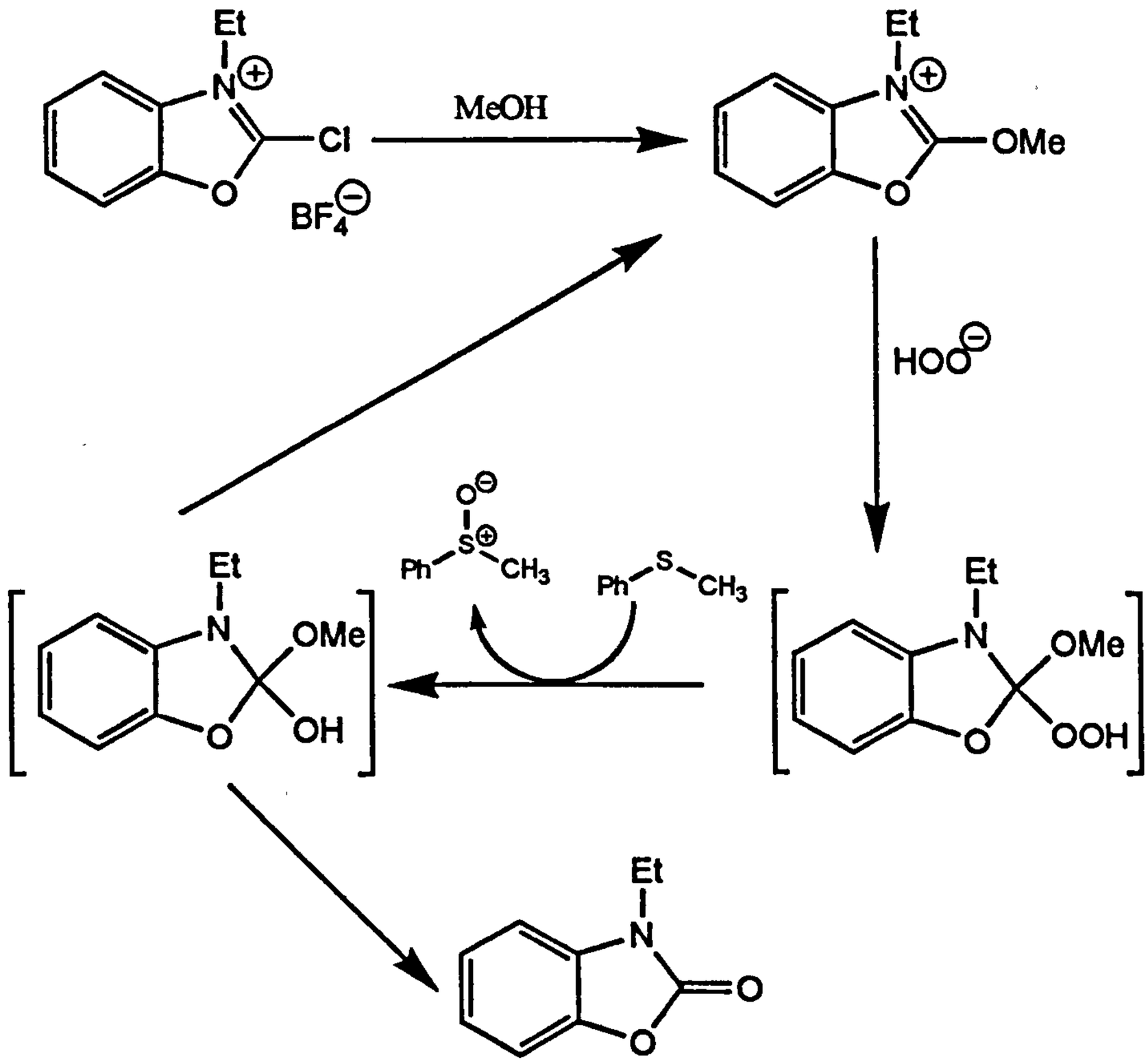
Scheme 5.15



Scheme 5.16

One other possibility that must be considered is that the addition product formed between **(41)** and methanol can undergo nucleophilic addition by hydrogen

peroxide to yield an active oxidant (**Scheme 5.17**). After *O*-transfer, the product can either expel hydroxide to complete the catalytic cycle or lose methanol to form compound **(50)**.



Scheme 5.17

5.4 Conclusions

In the heterogeneous reactions at 25°C the 2-alkyl- and 2-aryl-benzoxazolium salts give a stoichiometric amount of sulfoxide; the rate of reaction is independent of sulfide concentration and is proportional to the concentration of the mediator. The mediator which gives the most phenyl methyl sulfoxide in 24 hours is 2-chloro-3-ethylbenzoxazolium tetrafluoroborate **(41)** (66 %). 2-Phenyl-3-methylbenzoxazolium tetrafluoroborate **(36)** and 3-methylbenzoxazolium tetrafluoroborate **(35)** yield approximately the same amount of sulfoxide (32 and 33 %). 2-*t*-Butyl-3-methylbenzoxazolium tetrafluoroborate **(37)** and 2,3-dimethylbenzoxazolium tosylate **(47)** both give 29 % phenyl methyl sulfoxide. The 2-alkyl- and 2-aryl-benzoxazolium salts were all transformed into the corresponding *o*-amidophenols

under the reaction conditions; compound **(41)** was converted to 2-ethylbenzoxazolinone **(50)**.

2-Methyl-3,4-dihydroisoquinolinium tosylate **(54)**, which has previously been shown to epoxidise olefins and sulfides, proved under the standard conditions to have the same activity as the 2-alkyl-benzoxazolium salts (or slightly less). This indicates that under alternative reaction conditions these mediators may be useful for the oxidation of nucleophilic compounds such as sulfides and olefins.

Compound **(41)** (2-Cl) acts most effectively for thioanisole oxidation under conditions of low hydrogen peroxide concentration; when the concentration is increased (in either the heterogeneous or homogeneous reactions) the conversion of thioanisole is reduced significantly due to increased decomposition of the mediator. Almost complete conversion of thioanisole is achieved within 24 hours, if an equimolar amount of **(41)** is used, along with a low peroxide concentration. 2-Phenyl-benzoxazolium salt **(36)** is the best mediator of sulfide oxidation when a high concentration of H_2O_2 is present, giving 70 % conversion in 24 hours.

The mechanism proposed for these oxidations is shown in **Scheme 5.3** and leads to the integrated rate equation **[14]**. The data obtained in the heterogeneous reactions give linear plots of *ln* $\{[S] - [S]_\infty\}$ against time, supporting **Scheme 5.3** as the mechanism of the reaction.

The benzothiazolium salts are all inferior mediators of *O*-transfer compared to the corresponding benzoxazolium salts. 3-Methylbenzothiazolium tetrafluoroborate **(38)** gives the most phenyl methyl sulfoxide (23 %); 2,3-dimethylbenzothiazolium tosylate **(56)** yields 16 %. 2-Phenyl-3-methylbenzothiazolium tetrafluoroborate **(39)** and 2-*tert*-butyl-3-methylbenzothiazolium tetrafluoroborate **(40)** only give 11 and 12 % sulfoxide respectively. The decomposition products of the 2-alkyl- and 2-aryl-benzothiazolium salts, *o*-amidothiophenols, are oxidised to disulfides under the reaction conditions.

1, 3-Dimethyl-2-phenylbenzimidazolium tetrafluoroborate **(43)**, 1, 3-dimethyl-2-*t*-butylbenzimidazolium tetrafluoroborate **(42)** and 1,2,3,3-tetramethyl-3*H*-indoleninium tetrafluoroborate **(44)** all show no (or very little) activity over the uncatalysed reaction. It is proposed that the benzimidazolium salts do not form addition products with hydrogen peroxide due to delocalisation of the iminium positive charge over two nitrogen atoms. 1,2,3,3-Tetramethyl-3*H*-indoleninium

tetrafluoroborate **(44)** is converted under the reaction conditions to 1,3,3 trimethyloxindole **(61)**.

The neutral compound 3-*tert*-butyl-1,2-benzisothiazole 1,1-dioxide **(65)** acted catalytically under the reaction conditions, giving 36 % sulfoxide in the first 24 hours and a further 27 % in the next 24 hours. The active oxidant in this case is an α-hydroperoxyamine.

At the higher temperature of 40°C, 2-chloro-3-ethylbenzoxazolium tetrafluoroborate **(41)** was again the best mediator giving 70 % sulfoxide after 24 hours. 2-*t*-Butyl-3-methylbenzoxazolium tetrafluoroborate **(37)** and 3-methylbenzoxazolium tetrafluoroborate **(35)** yield approximately the same amount of sulfoxide (52 and 50 %). Significantly, this is more than a stoichiometric amount of sulfoxide even when taking into account the background reaction. 2-Phenyl-3-methylbenzoxazolium tetrafluoroborate **(36)** is the poorest mediator and gives a stoichiometric amount of sulfoxide at this temperature (allowing for that produced in the uncatalysed oxidation).

The homogenous reactions give linear structure-activity relationships with negative ρ values for all of the benzoxazolium salts tested. 2-*t*-Butyl-3-methylbenzoxazolium tetrafluoroborate **(37)** is the compound most influenced by the substituents in the aromatic ring of thioanisole. The magnitude of the ρ value (-1.6) obtained for this compound supports the case that the active oxidant for the 2-alkyl- and 2-aryl-benzoxazolium salts is an α-hydroperoxyamine.

2-Chloro-3-ethylbenzoxazolium tetrafluoroborate **(41)** was shown to be the least selective of the salts, based on the ρ values obtained. The active oxygen transfer agent is a very powerful oxidant, having a similar value to that obtained for dimethyl dioxirane; the nature of this species is as yet unconfirmed. It appears that this species is decomposed by hydrogen peroxide, since when the concentration of peroxide is increased the amount of sulfoxide formed decreases significantly in this case.

The interpretation of the results obtained for the oxidations is equivocal; more data is necessary before any definite conclusions about the reaction mechanisms can be made. The complex nature of the reaction mechanism means that some assumptions made in the derivation of the integrated rate equation are not always valid and this means that determination of the actual rate constants is made difficult.

In the following chapter, some of the benzoxazolium and benzothiazoloum salts will be tested as activators of hydrogen peroxide in hard-surface cleaning applications.

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Chapter 6

The Use Of Iminium Salts

For Hard Surface Cleaning Applications

6.1 Introduction

Certain soils and household stains, for example: pigmented mould, food residues and WC stains can only be removed effectively by bleaching. The most effective, commercially available bleach for household cleaning is sodium hypochlorite. An alternative is necessary because of human and environmental safety issues and because its pungent, irritating odour makes it unpleasant to use.

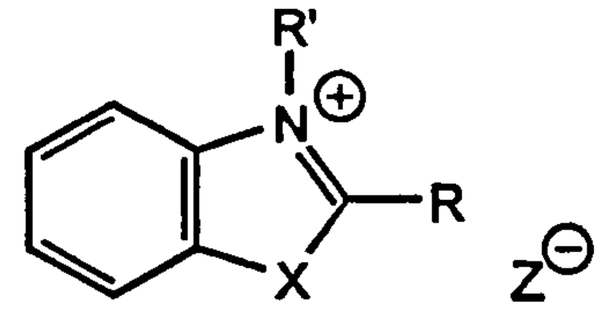
Sodium hypochlorite is a very powerful nucleophile and oxidising agent and as such it can decolourise pigments (such as mildew, wine, tea, etc.), break up soil matrices (e.g. baked on cooker-hob soil) and kill microorganisms (WC, food preparation surfaces). Sodium hypochlorite is extremely efficient at soil removal and stain decolourisation; it is a broad spectrum biocide and is highly cost effective.

Recently, however environmental concerns have led to calls for a reduction in the use of chlorine and chlorinated compounds. In 1991, the international environmental advocacy group Greenpeace, called for the complete phasing out of "the use, export and import of all organochlorines, elemental chlorine, and chlorinated oxidising agents (e.g. chlorine dioxide and sodium hypochlorite)".[1] At the beginning of 1994, US president Clinton introduced a Clean Water Initiative to develop a "national strategy for substituting, reducing or prohibiting the use of chlorine and chlorinated compounds".[2] Sodium hypochlorite is acutely toxic to aquatic life and vegetation; furthermore it can react with organic matter in water and sewage to form toxic by-products such as trihalomethanes, halogenated acetic acids, chlorinated ketones, chlorinated furanones and other organochlorines. Although these substances are normally present only in the range of parts per billion (ppb), they have caused considerable concern because several of them are known or suspected carcinogens.[3, 4] The United States Environmental Protection Agency established 0.10 mg/ L as the maximum trihalomethane containment level for drinking water in July 1991.[5]

Also there are other general safety concerns: sodium hypochlorite is extremely reactive and if it is mixed with other cleaning products a mixture of toxic gases can be liberated (see **Section 1.4.1**).

This chapter deals with the appraisal of studies of 2-substituted-benzothiazolium (X = S; **(28)**) and 2-substituted-benzoxazolium (X = O; **(29)**) salts in conjunction with hydrogen peroxide for hard surface cleaning. This appraisal

involved monitoring the ability of these systems to remove two types of model soil: curcumin-oil on formica tiles and mould paste on unglazed kitchen tiles.



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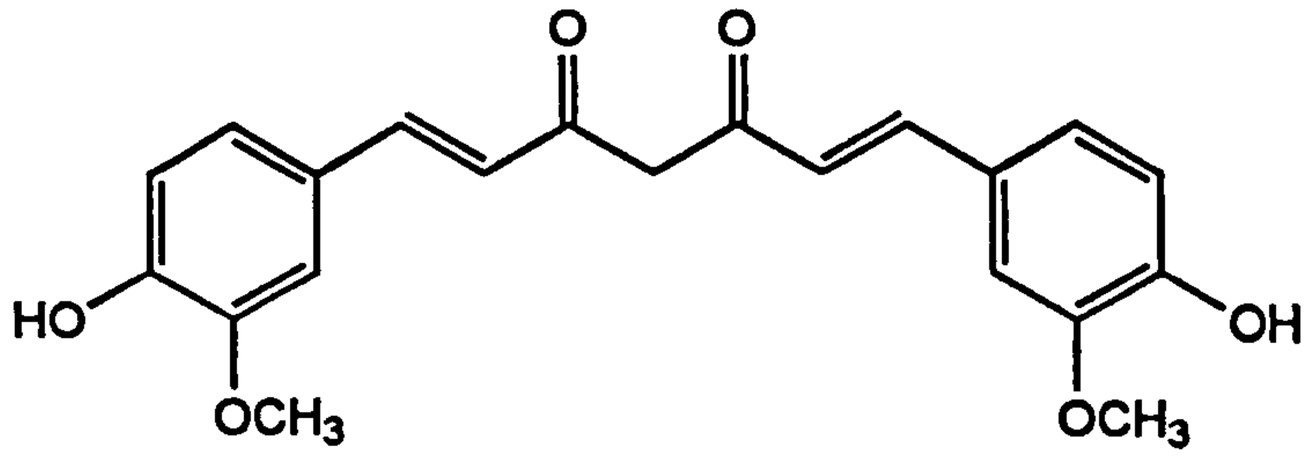

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6.2 Bleaching Of Curcumin-Oil On Formica Tiles

6.2.1 Preparation Of Stain Model

Sunflower oil (9.50 g) was mixed with curcumin **(73)** (0.50 g) *bis*-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione in a 150 cm^3 beaker and stirred for at least five minutes. Ethanol (90.0 g) was added to the mixture (washing any curcumin from the sides of the beaker) and the mixture was then stirred for at least ten minutes (until homogenous). Twenty-four standard formica tiles (90 x 125 mm^2) were washed with methanol and wiped dry with paper tissue.

The tiles were stacked vertically at the rear of a fume-hood and the homogenous curcumin-oil solution was poured into a gravity-feed spray-gun connected to a compressor. The solution was then sprayed onto the tiles as evenly as possible using the spray-gun connected to the compressor at 35 psi. The tiles were sprayed in groups of three or four and the solution was returned to the beaker for stirring between groups. The tiles were laid flat on a bench to dry for at least two hours to produce a slightly tacky yellow coloured oil film. The tiles were used on the day of their preparation since photobleaching is known to occur.

6.2.2 Preparation Of Bleaching Systems

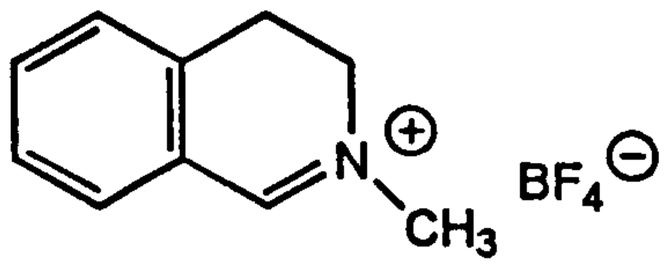
3 % H_2O_2

Hydrogen peroxide (35 % (w/v); 8.57 g;) and Dequest 2047 (0.018 g) were dissolved in distilled water (approximately 70 cm^3). The pH was measured using a

pH meter and adjusted to 10.50 by the addition of 1.0 M sodium hydroxide solution. Distilled water was then added until the total volume was 100 cm^3.

3% H_2O_2 / 1% (w/w) 2-Methyl-3,4-dihydroisoquinolinium tetrafluoroborate (54)

Hydrogen peroxide (35 % (w/v); 8.57 g; 88.19 mmol; 28.0 eq) and Dequest 2047 (0.018 g) were added to **(54)** (1.06g; 3.15 mmol; 1.0 eq) and dissolved in distilled water (approximately 70 cm^3). The pH was measured using a pH meter and adjusted to 10.50 by the addition of 1.0 M sodium hydroxide solution. Distilled water was then added until the total volume was 100 cm^3.



(54)

3% H_2O_2 / ~1% (w/w) benzoxazolium / benzothiazolium salt

Hydrogen peroxide (35 % (w/v); 8.57 g; 88.19 mmol; 28.0 eq) and Dequest 2047 (0.018 g) were dissolved in distilled water (approximately 70 cm^3). The pH was measured using a pH meter and adjusted to 10.60 by the addition of 1.0 M sodium hydroxide solution. This solution was then added in one portion to the salt under investigation (3.15 mmol; 1.0 eq) and the solution made up to 100 cm^3 with distilled water and used immediately. If less salt was available then the other components were reduced to the appropriate amounts.

6.2.3 Procedure for stain removal

A glass ring (46 mm diameter) was placed at the centre of a tile and the bleach system under investigation (5 cm^3) was poured into the ring via a pipette. After allowing thirty seconds contact time the fluid was washed away with deionised water.

6.2.4 Assessment Of Soil Removal

Ten trained panelists were asked to score each tile from zero to five using a half-integer scale (zero indicating no soil removal and five complete removal) referring to a set of standard photographs. This data was then statistically analysed

(using a Statistical Analysis System (SAS)) to yield a mean value for soil removal with 95% confidence limits.

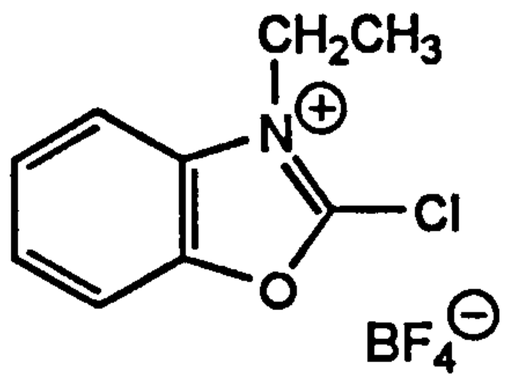
6.2.5 Results

The mean scores for soil removal of each bleaching system are shown in the following data; the standard deviation and 95% confidence interval for each score are also shown in the corresponding tables.

The first two tables show the initial assessment of 2-substituted-benzoxazolium salts **(41)**, **(37)**, **(35)**, and **(47)** in conjunction with hydrogen peroxide, for the removal of curcumin-oil stains from formica tiles. The assessment was carried out at pH 10.5 since in a separate study[6] of compound **(54)** this was shown to give the optimum performance over alkaline peroxide alone. Also shown is the performance of the same bleaching systems after the mixtures were allowed to stand for ten minutes; this gives a representation of the stability of the salts to the alkaline, oxidising conditions employed. The ability of **(37)** to remove soil with an equimolar amount of peroxide is also shown in **Table 6.2** (entry 3).

Table 6.3 shows a repeat run using compound **(35)** since at first it appeared to be more active than peroxide alone. It also shows assessment of compounds **(37)** and **(35)** at pH 10 since limiting alkali levels is important commercially and at these reduced levels the salts might be more stable and so give better soil removal.

Table 6.4 shows the assessment of 2-substituted-benzothiazolium salts in conjunction with hydrogen peroxide, for the removal of curcumin-oil stains from formica tiles.



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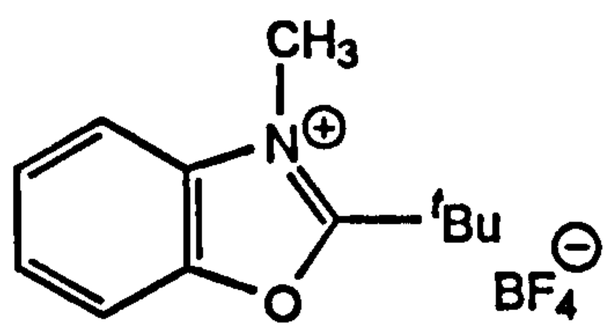


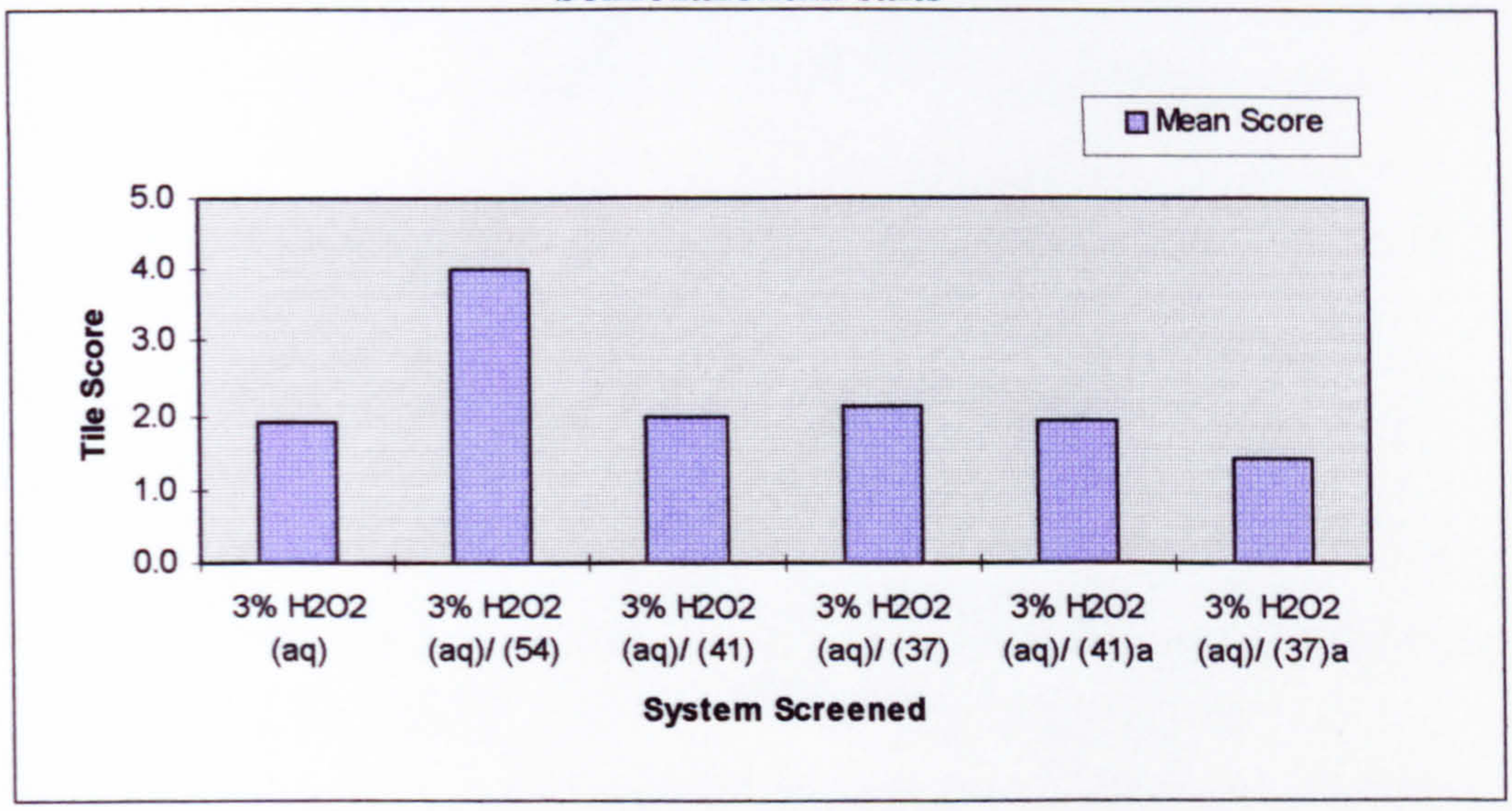
(37)

Table 6.1 Bleaching of curcumin-oil on formica tiles by 2-substituted-benzoxazolium salts

Entry	System	pH	Mean Score	Standard Deviation	95% Confidence Interval
1	3% H_2O_2(aq)	10.5	1.9	0.882	(1.59: 2.24)
2	3% H_2O_2(aq)/ **(54)**	10.5	4.0	0.771	(3.69: 4.34)
3	3% H_2O_2(aq)/ **(41)**	10.5	2.0	0.681	(1.64: 2.29)
4	3% H_2O_2(aq)/ **(37)**	10.5	2.1	1.246	(1.81: 2.46)
5	3% H_2O_2(aq)/ **(41)**[a]	10.5	1.9	0.671	(1.45: 2.25)
6	3% H_2O_2(aq)/ **(37)**[a]	10.5	1.4	0.990	(1.03: 1.82)

[a] The mixture was allowed to stand for 10 mins before use

Graph 6.1 Bleaching of curcumin-oil on formica tiles by 2-substituted-benzoxazolium salts



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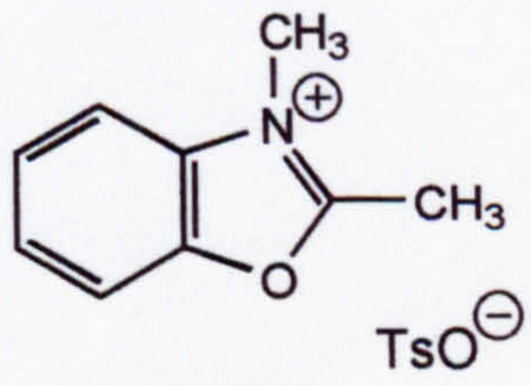


(47)

Table 6.2 Bleaching of curcumin-oil on formica tiles by 2-substituted-benzoxazolium salts

Entry	System	pH	Mean Score	Standard Deviation	95% Confidence Interval
1	3% H_2O_2(aq)/	10.5	2.0	0.635	(1.74: 2.27)
2	3% H_2O_2(aq)/ **(54)**	10.5	3.3	0.801	(3.01: 3.54)
3	0.1 % H_2O_2(aq)/ **(37)**	10.5	0.0	0.096	(-0.246: 0.283)
4	3% H_2O_2(aq)/ **(35)**	10.5	2.5	0.855	(2.24: 2.77)
5	3% H_2O_2(aq)/ **(47)**	10.5	1.6	0.827	(1.37: 1.90)
6	3% H_2O_2(aq)/ **(35)**[a]	10.5	0.9	0.464	(0.49: 1.40)
7	3% H_2O_2(aq)/ **(47)**[a]	10.5	1.4	0.782	(0.93: 1.85)

[a] The mixture was allowed to stand for 10 mins before use

Graph 6.2 Bleaching of curcumin-oil on formica tiles by 2-substituted-benzoxazolium salts

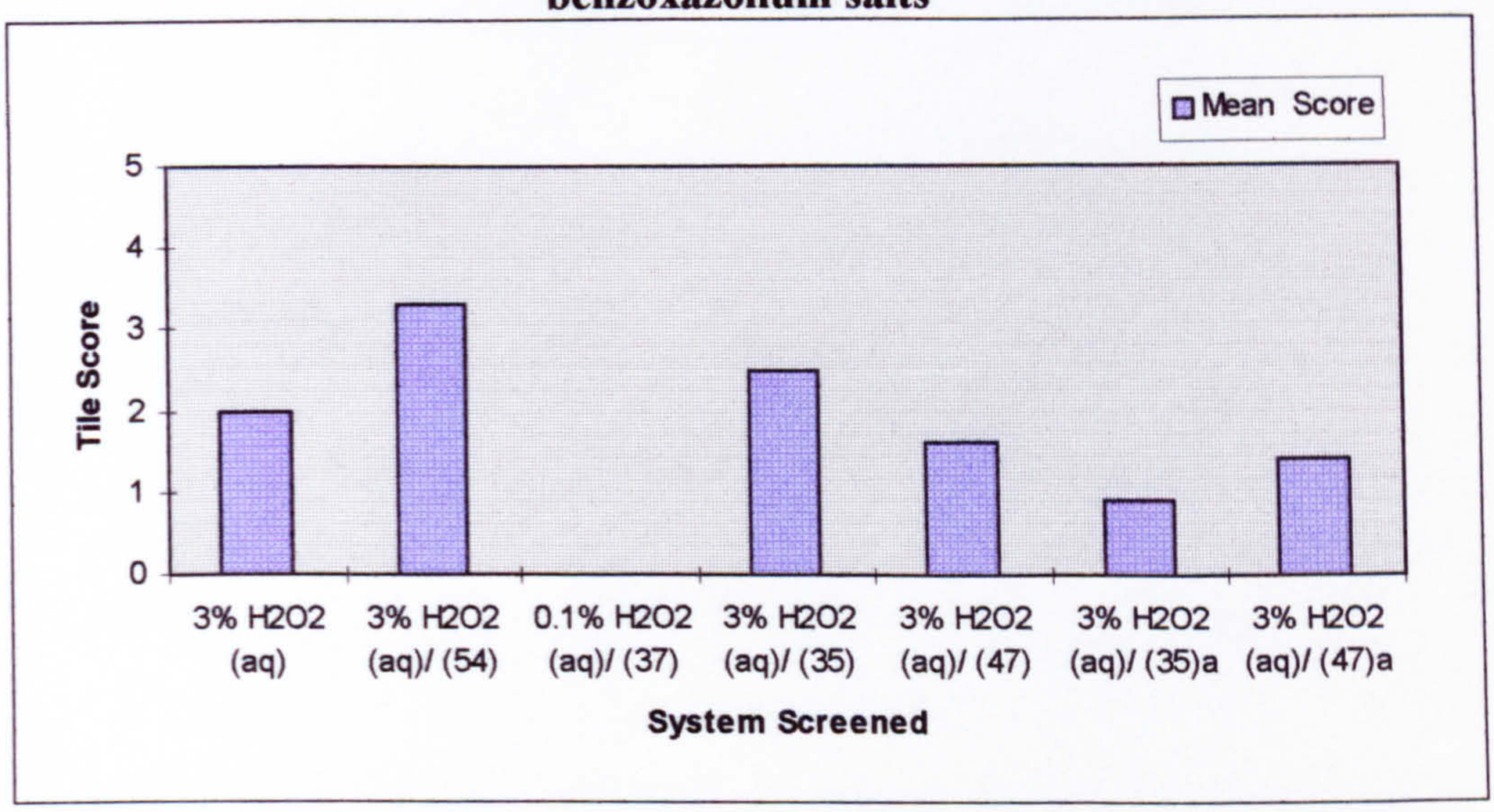
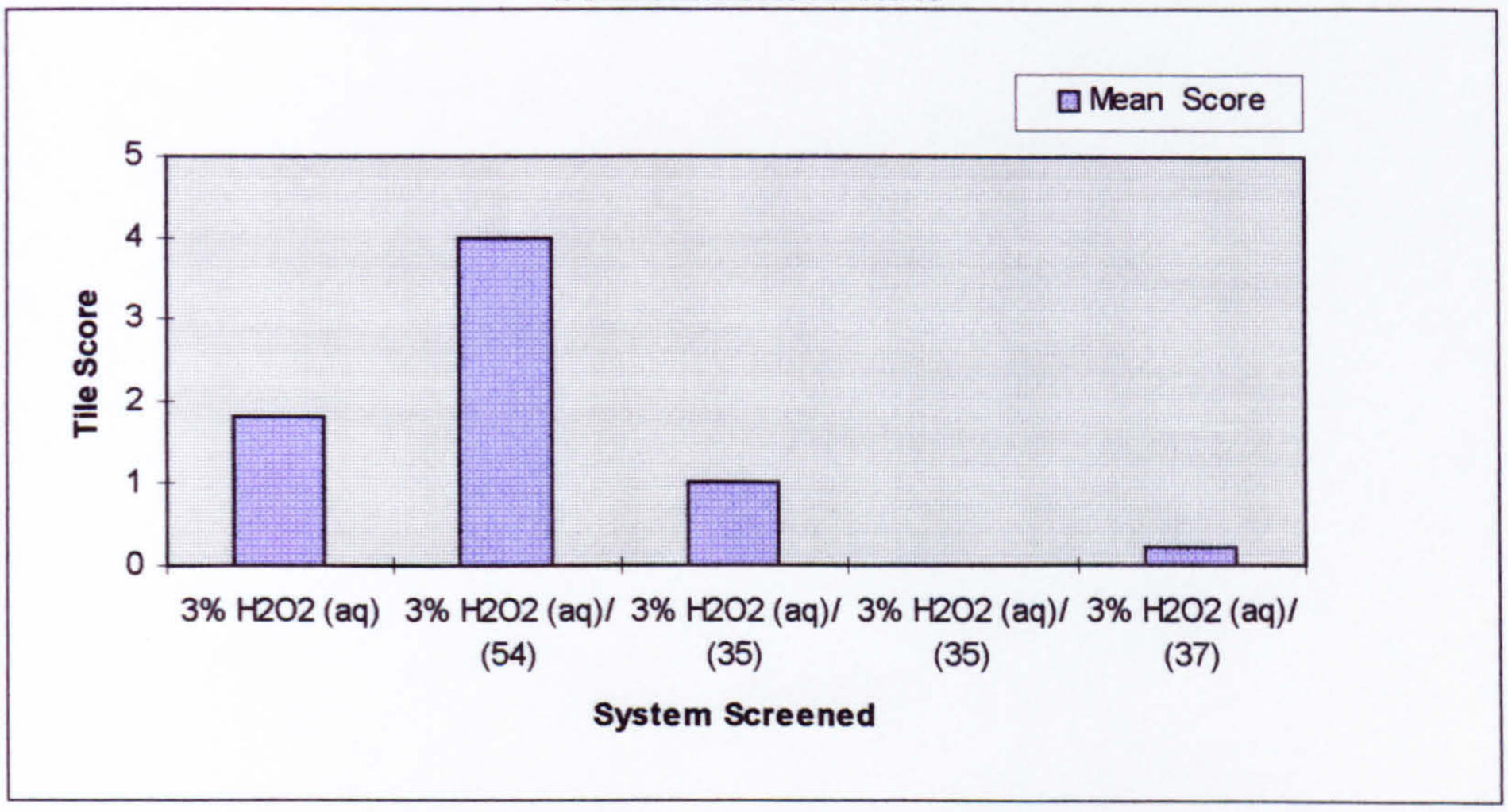
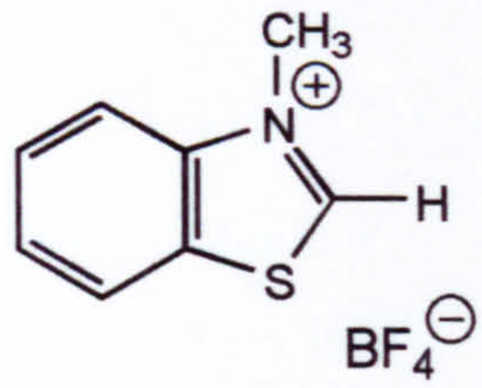


Table 6.3 Bleaching of curcumin-oil on formica tiles by 2-substituted-benzoxazolium salts at pH 10

Entry	*System*	*pH*	Mean Score	Standard *Deviation*	95% *Confidence* Interval
1	3% H_2O_2(aq)	10.5	1.8	0.73	*(1.64: 2.02)*
2	3% H_2O_2(aq)/ **(54)**	10.5	4.0	0.354	(3.81: 4.18)
3	3% H_2O_2(aq)/ **(35)**	10.5	1.0	0.432	(0.84: 1.21)
4	3% H_2O_2(aq)/ **(35)**	10	0.0	0.000	(-0.184: 0.184)
5	3% H_2O_2(aq)/ **(37)**	10	0.2	0.242	(-0.0174: 0.351)

Graph 6.3 Bleaching of curcumin-oil on formica tiles by 2-substituted-benzoxazolium salts





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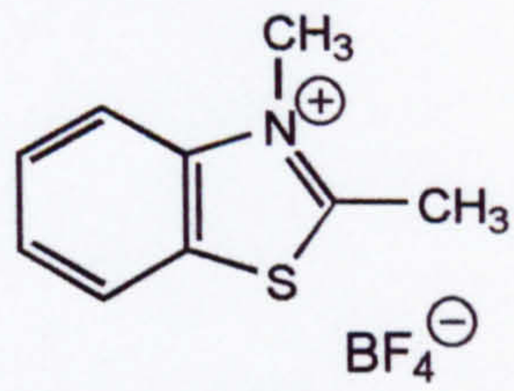

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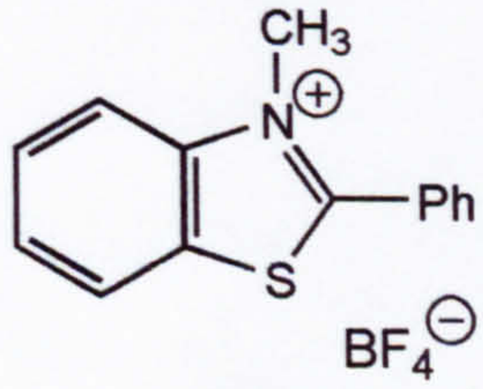
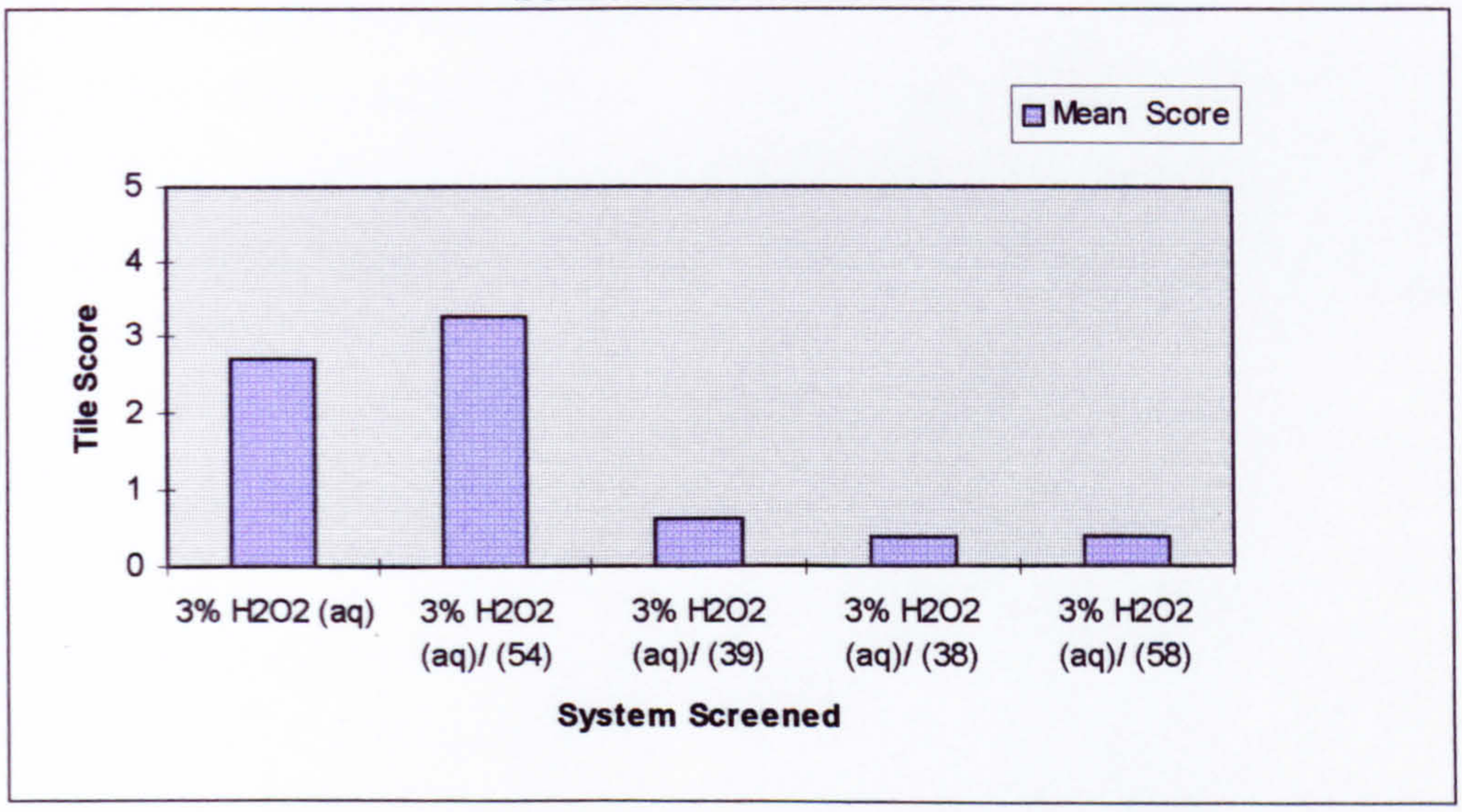


(39)

Table 6.4 Bleaching of curcumin-oil on formica tiles by 2-substituted-benzothiazolium salts

Entry	System	pH	Mean Score	Standard Deviation	95% Confidence Interval
1	3% H_2O_2(aq)/	10.5	2.7	0.685	(2.57: 2.91)
2	3% H_2O_2(aq)/ **(54)**	10.5	3.3	0.524	(3.13: 3.46)
3	3% H_2O_2(aq)/ **(39)**	10.5	0.6	0.359	(0.41: 0.74)
4	3% H_2O_2(aq)/ **(38)**	10.5	0.4	0.242	(0.24: 0.57)
5	3% H_2O_2(aq)/ **(58)**	10.5	0.4	0.181	(0.26: 0.59)

Graph 6.4 Bleaching of curcumin-oil on formica tiles by 2-substituted-benzothiazolium salts



6.2.6 Conclusions

None of the 2-substituted-benzoxazolium or 2-substituted-benzothiazolium salts screened for removal of curcumin-oil showed activity above that of hydrogen peroxide alone. The 2-substituted-benzothiazolium salts (**(38)**, **(58)**, **(39)**) were considerably less active than the corresponding 2-substituted-benzoxazolium salts (**Tables 6.1**, **6.2**, **6.4**).

Allowing the prepared bleaching solutions to stand for a short period (10 minutes) decreases the stain removing ability of the salts indicating that they are not stable to such an alkaline, oxidising environment (**Tables 6.1 & 6.2**). Reducing the level of hydrogen peroxide in solution to an equimolar amount (with respect to mediator) reduced bleaching by **(37)** to negligible levels (**Table 6.2**, entry 3).

Lowering the pH of the bleaching mixture from 10.5 to 10.0 decreases the activity of the benzoxazolium salts to virtually nil (**Table 6.3**, entries 4 and 5).

6.3 Mould paste on unglazed ceramic tiles

6.3.1 Preparation of mould paste

Black hyphae from *Cladosporium cladosporides* were autoclaved and then mixed with a little distilled water and crushed into a smooth paste using a pestle and mortar. The paste consisted of a mixture of fine particles of hyphal cell wall and a black mould ink.

6.3.2 Preparation of tiles

The unglazed ceramic tiles were soaked in dilute Domestos® Multi Surface Cleaner for three to five hours and then soaked in water overnight to remove any traces of bleach. The tiles were then allowed to dry at room temperature for half a day. The mould paste was then smoothed over the porous tiles to give a uniform dark grey / black stain. After allowing the tiles to dry at room temperature overnight, they were cut into small pieces (approximately 25 x 25 mm^2).

6.3.3 Procedure for stain removal

A small circular piece of single-ply tissue paper (17 mm diameter) was placed on the surface of the stained tile. One drop of the bleaching solution under investigation was pipetted on to the tissue paper and then allowed to stand for three minutes. The oxidant was then quenched by immersing the tile in 1.0 M sodium thiosulfate solution for at least ten minutes and then rinsed with distilled water. The tiles were then allowed to dry on paper towelling.

6.3.4 Assessment Of Soil Removal

Ten trained panelists were asked to score each tile from zero to six using a half-integer scale (zero indicating no soil removal and six complete removal) referring to a set of standard photographs. This data was then statistically analysed (using a SAS program) to yield a mean value for soil removal with 95% confidence limits.

6.3.5 Results

The mean scores of each bleaching system are shown in the following data; the standard deviation and 95% confidence interval for each score are shown in the corresponding tables.

The first two tables (**Table 6.5** & **Table 6.6**) show the initial assessment of 2-substituted-benzoxazolium salts **(41)**, **(37)**, **(35)**, and **(47)** in conjunction with hydrogen peroxide, for the removal of mould paste from unglazed ceramic tiles. Also shown is the performance of **(41)** and **(37)** after the mixtures were allowed to stand for ten minutes; this gives a representation of the stability of the salts to the alkaline, oxidising conditions employed. The ability of **(37)** to remove soil with an equimolar amount of peroxide is also shown in **Table 6.6**. Also shown is the performance of **(37)** at pH 11.0 because it has been demonstrated previously that compound **(54)** gives better performance at this pH.

Table 6.7 illustrates the assessment of 2-substituted-benzothiazolium salts in conjunction with hydrogen peroxide, for the removal of mould paste from unglazed ceramic tiles.

Table 6.8 shows the ability of **(37)** and **(35)** to remove mould paste from unglazed ceramic tiles at pH 10 because limiting alkali levels is important commercially and at these reduced levels of alkali they might have been more stable and give better soil removal. Also shown is the performance of **(35)** with double the amount of mediator added to the bleaching solution.

Table 6.5 Bleaching of mould paste by 2-substituted-benzoxazolium salts

Entry	System	pH	Mean Score	Standard Deviation	95% Confidence Interval
1	3% H_2O_2(aq)	10.5	1.2	0.424	(0.61: 1.87)
2	3% H_2O_2(aq)/ **(54)**	10.5	2.7	3.893	(2.04: 3.54)
3	3% H_2O_2(aq)/ **(41)**	10.5	1.1	0.487	(0.48: 1.74)
4	3% H_2O_2(aq)/ **(37)**	10.5	2.2	0.559	(1.57: 2.84)
5	3% H_2O_2(aq)/ **(41)**[a]	10.5	1.4	0.664	(0.74: 2.00)
6	3% H_2O_2(aq)/ **(37)**[a]	10.5	1.6	0.515	(0.92: 2.18)

[a] The mixture was allowed to stand for 10 mins before use

Graph 6.5 Bleaching of mould paste by 2-substituted-benzoxazolium salts

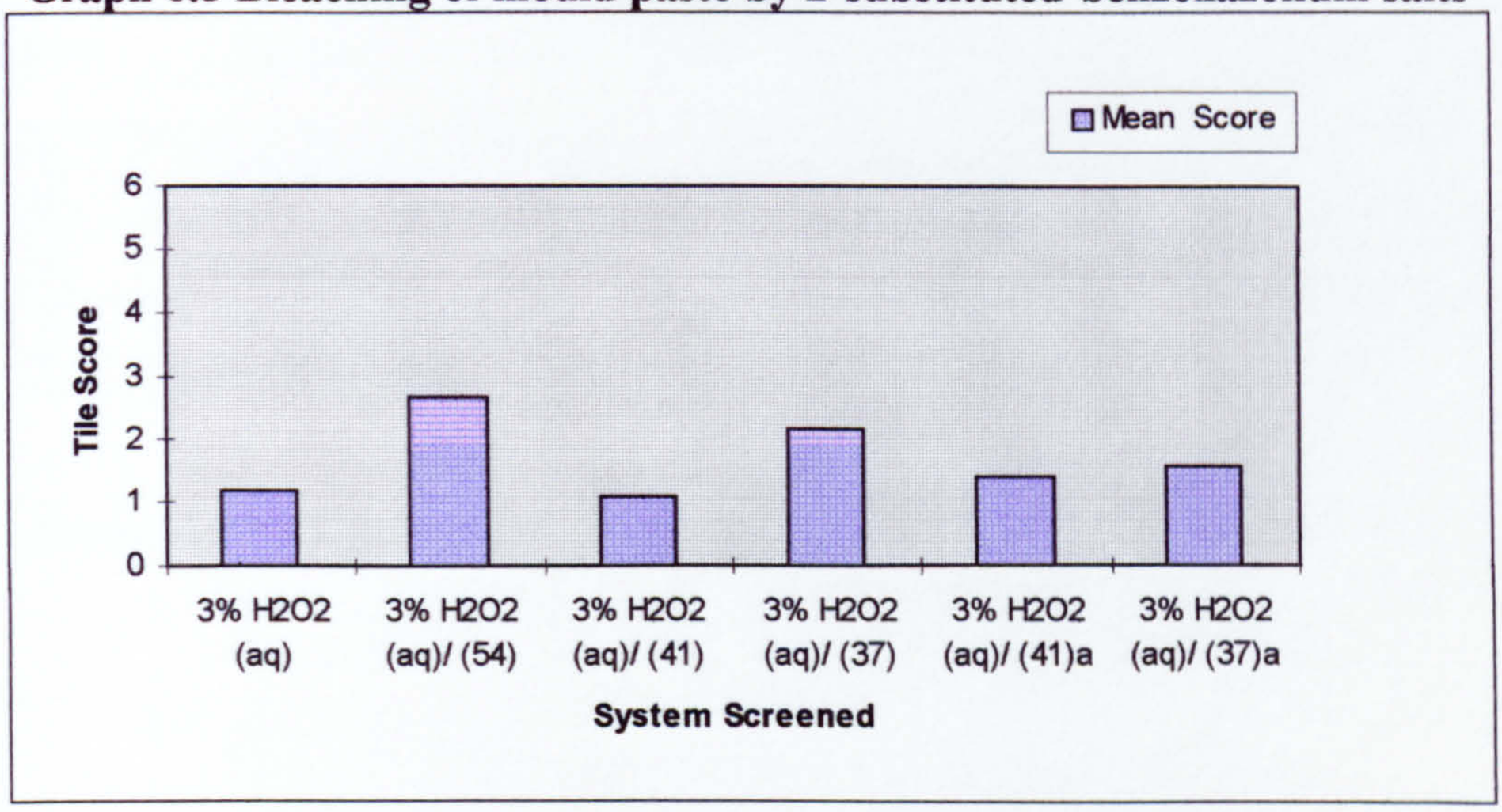


Table 6.6 Bleaching of mould paste by 2-substituted-benzoxazolium salts

Entry	System	pH	Mean Score	Standard Deviation	95% Confidence Interval
1	3% H_2O_2(aq)	10.5	1.0	0.499	(0.87: 1.20)
2	3% H_2O_2(aq)/ **(54)**	10.5	1.7	0.572	(1.50: 1.83)
3	0.1 % H_2O_2(aq)/ **(37)**	10.5	0.0	0.133	(-0.13: 0.20)
4	3% H_2O_2(aq)/ **(35)**	10.5	0.6	0.385	(0.41: 0.74)
5	3% H_2O_2(aq)/ **(47)**	10.5	0.4	0.301	(0.26: 0.59)
6	3% H_2O_2(aq)/ **(37)**	11.0	1.5	0.553	(1.37: 1.70)

Graph 6.6 Bleaching of mould paste by 2-substituted-benzoxazolium salts

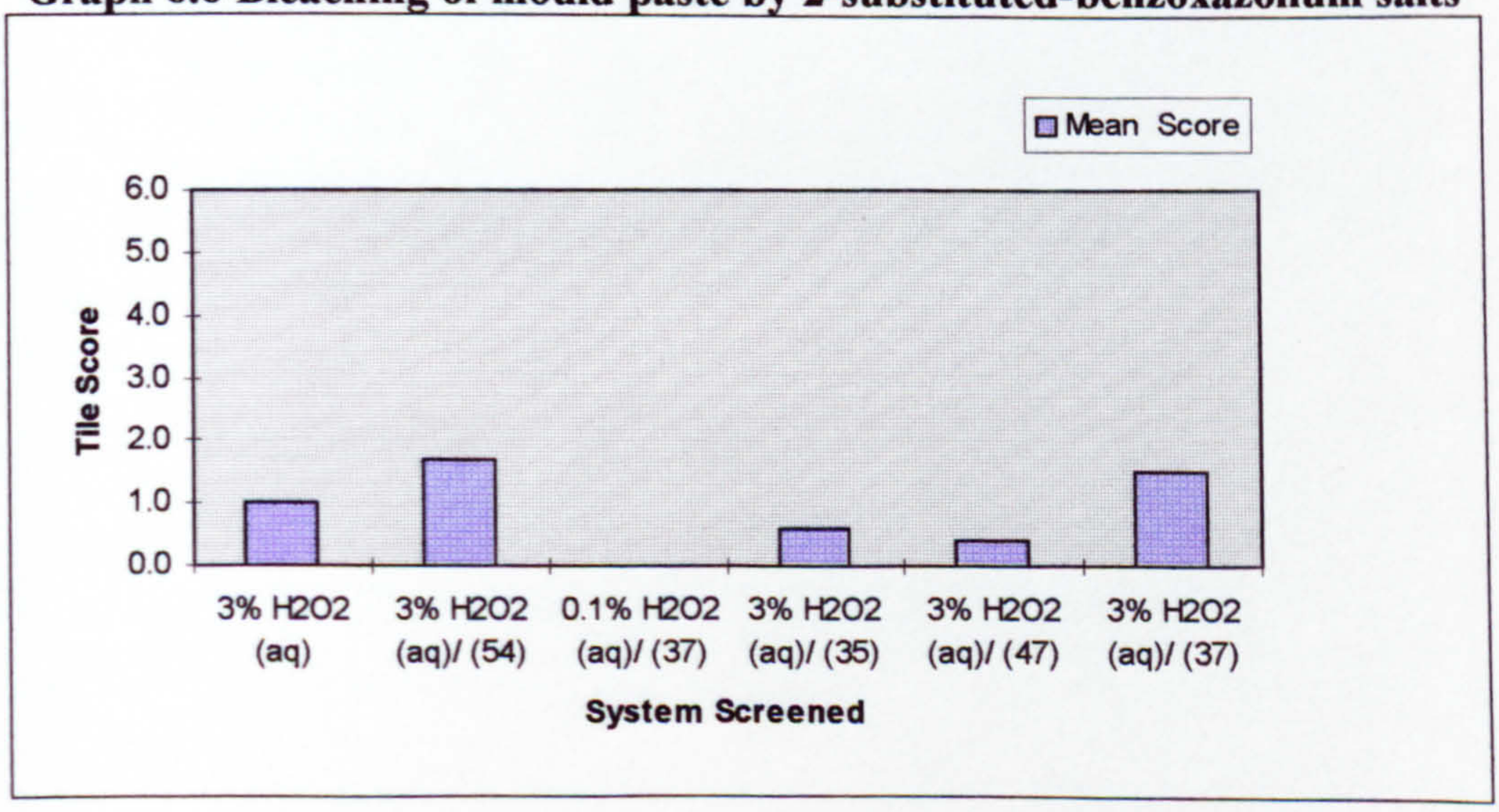


Table 6.7 Bleaching of mould paste by 2-substituted-benzothiazolium salts

Entry	System	pH	Mean Score	Standard Deviation	95% Confidence Interval
1	3% H_2O_2(aq)	10.5	0.48	0.379	(0.35: 0.62)
2	3% H_2O_2(aq)/ **(54)**	10.5	0.87	0.451	(0.74: 1.00)
3	3% H_2O_2(aq)/ **(39)**	10.5	0.56	0.424	(0.42: 0.69)
4	3% H_2O_2(aq)/ **(38)**	10.5	0.07	0.181	(0.06: 0.21)
5	3% H_2O_2(aq)/ **(58)**	10.5	0.17	0.240	(0.03: 0.30)

Graph 6.7 Bleaching of mould paste by 2-substituted-benzothiazolium salts

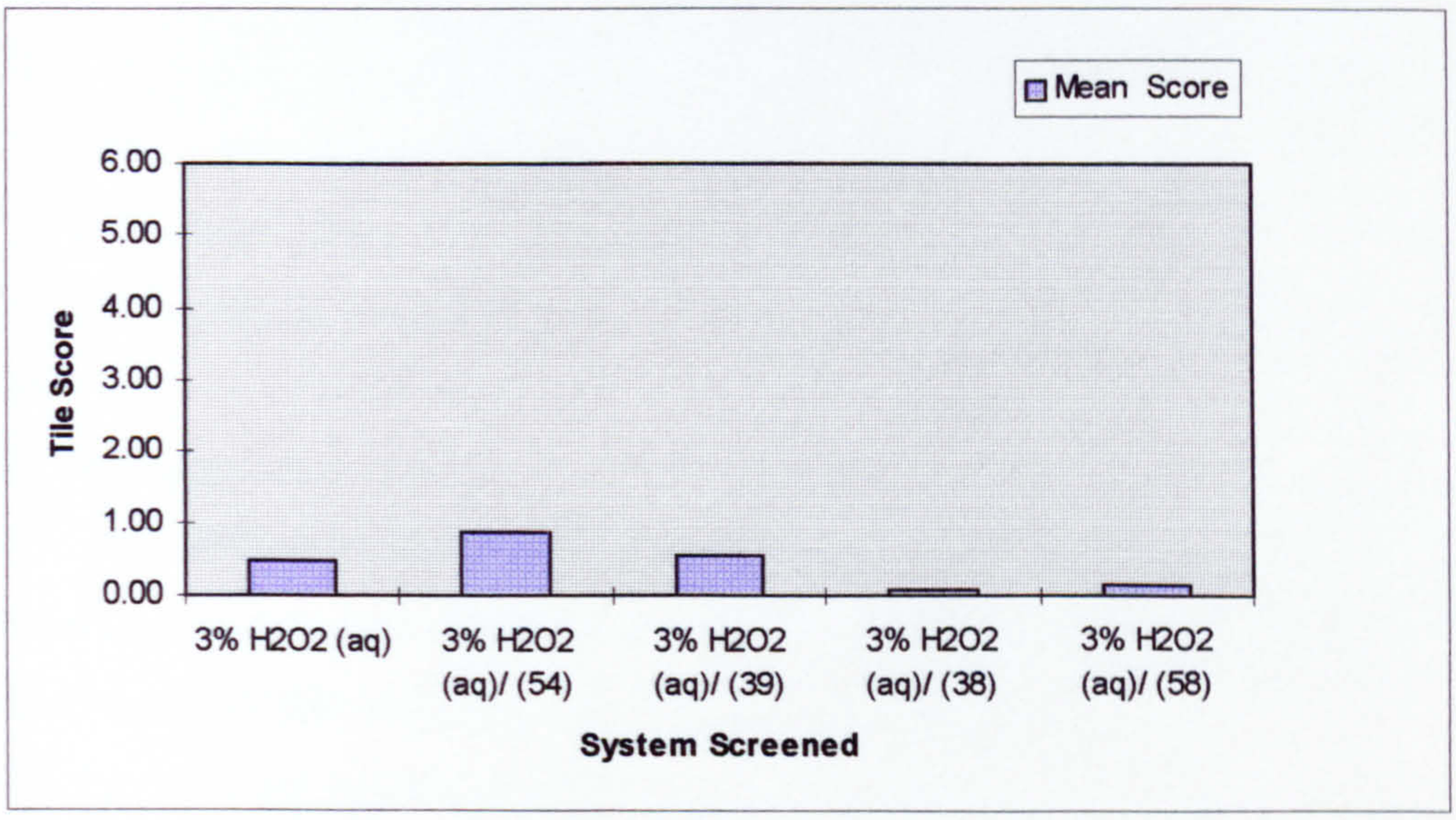
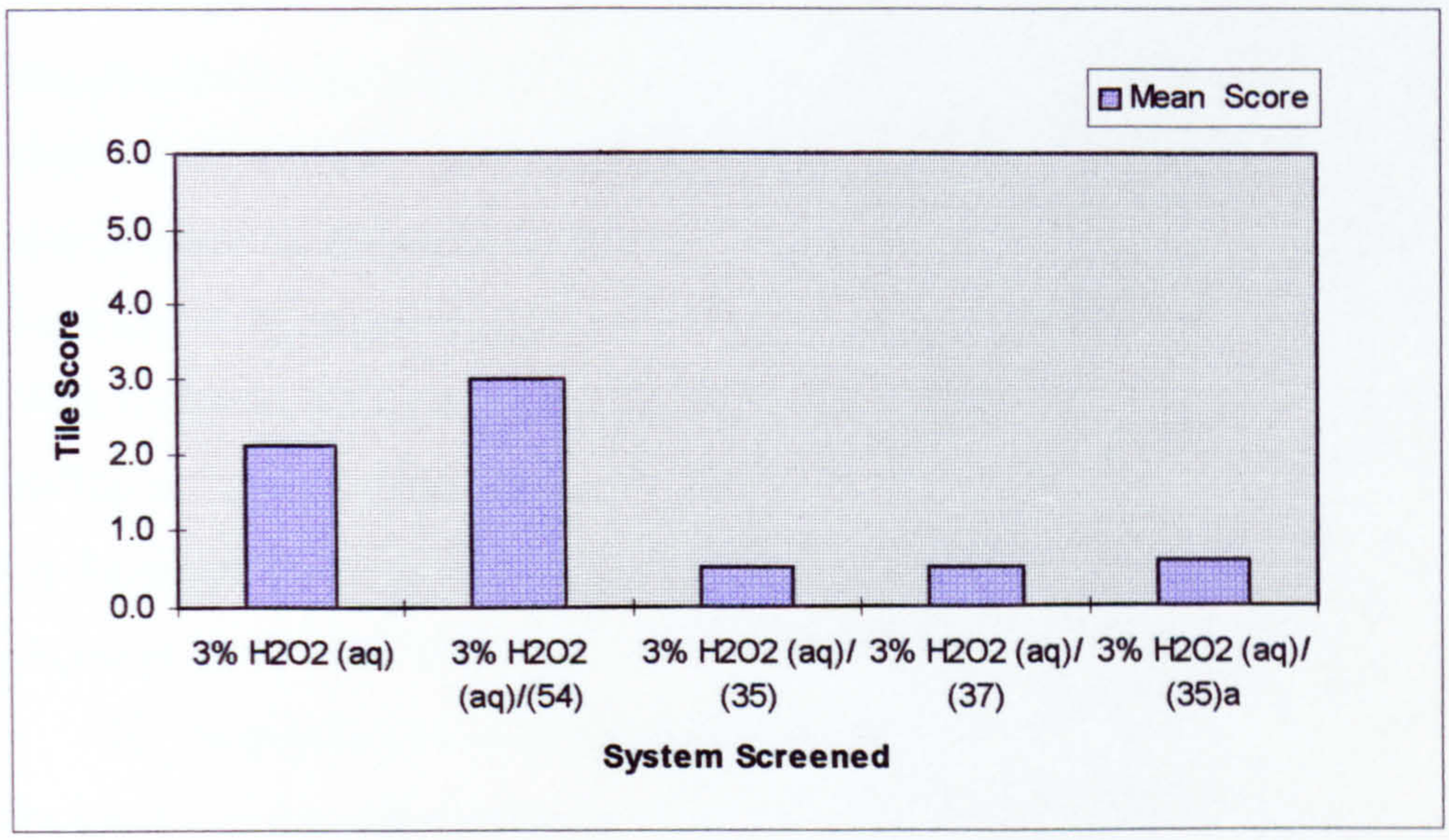


Table 6.8 Bleaching of mould paste by 2-substituted-benzoxazolium salts at pH 10.0

Entry	System	pH	Mean Score	Standard Deviation	95% Confidence Interval
1	3% H_2O_2(aq)	10.5	2.1	0.937	(1.87: 2.40)
2	3% H_2O_2(aq)/ **(54)**	10.5	3.0	0.873	(2.70: 3.25)
3	3% H_2O_2(aq)/ **(35)**	10.0	0.50	0.224	(0.22: 0.78)
4	3% H_2O_2(aq)/ **(37)**	10.0	0.52	0.536	(0.25: 0.80)
5	3% H_2O_2(aq)/ **(35)**[a]	10.5	0.60	0.256	(0.32: 0.87)

[a] Double the amount of mediator was used.

Graph 6.8 Bleaching of mould paste by 2-substituted-benzoxazolium salts at pH 10.0



6.3.6 Conclusions

Only **(37)** (R = *t*-Bu; X = O) showed activity for the removal of mould paste above that of hydrogen peroxide alone; however this system was less effective than **(54)** (**Table 6.5**). Allowing the prepared bleaching solutions to stand for a short period (10 minutes) decreases the stain removing ability of **(37)** indicating that this salt is not stable to such an alkaline, oxidising environment; the performance of **(41)** is the same within experimental error.

Reducing the level of hydrogen peroxide in solution to an equimolar amount (with respect to mediator) reduced bleaching by **(37)** to negligible levels (**Table 6.6**, entry 3). At pH 11.0, soil removal by **(37)** was comparable to that by **(54)** at pH 10.5, but this increase in efficacy is probably caused by the change in pH (entry 6).

The 2-substituted-benzothiazolium salts tested for the removal of mould paste were less active than the corresponding 2-substituted-benzoxazolium salts (**Table 6.7**) and considerably less active than compound **(54)**.

Lowering the pH of the bleaching systems to pH 10.0 does not increase their stain removing ability; in fact the power of the best system **(37)** is reduced at this pH when compared to pH's 10.5 and 11.0 (**Table 6.5**, **6.6** & **6.8**). Doubling the concentration of **(35)** does not alter its performance (**Table 6.8**, entry 5 & **Table 6.6**, entry 4).

6.4 Conclusions

A range of 2-substituted benzoxazolium, benzothiazolium and benzimidazolium salts have been synthesised using known methods under simple reaction conditions and readily available starting materials. These compounds were used to mediate the oxidation of thioanisole by the activation of hydrogen peroxide. The commercially available 2-chlorobenzoxazolium salt **(41)** proved to be the most efficient mediator, giving complete conversion of sulfide when used in equimolar quantities at 25°C or when present in 25 mol % at 40°C. 2-Methyl-3,4-dihydroisoquinolinium tosylate **(54)**, known to be active for hard-surface cleaning applications, gave only 76 % conversion at 25°C.

The mechanism of *O*-transfer from hydrogen peroxide to *p*-substituted thioanisoles was investigated by, firstly, measuring the effect of initial reagent concentration on reaction rate, and then by deriving a quantitative-structure activity relationship based on Hammett's equation. The data collected point to a complex reaction mechanism, with the mediators acting catalytically in the sulfide oxidation, but being gradually depleted by a combination of processes. For the 2-alkyl and 2-aryl-benzoxazolium salts the active *O*-transfer agent appears to be an α-hydroperoxyamine, which is transformed in the process of oxygen transfer to an α-hydroxyamine. Two pathways are then available to this species; either the benzoxazolium salt is reformed, or the α-hydroxyamine is converted to an unknown intermediate, which is transformed to an *o*-amidophenol after work-up. 2-Chloro-3-ethylbenzoxazolium tetrafluoroborate seems to act catalytically in the oxidation of sulfides, whilst being gradually transformed to compound **(50)**; the active oxidant is not known in this case.

Some of the benzoxazolium and benzothiazolium salts were tested as activators of hydrogen peroxide in hard surface cleaning applications: bleaching of curcumin-oil mixtures and the removal of mould paste from kitchen tiles. None of the salts was effective at bleaching curcumin-oil mixtures, giving performance equal to unactivated hydrogen peroxide. 2-*t*-Butyl-3-methylbenzoxazolium tetrafluoroborate **(37)** was better than hydrogen peroxide at removal of mould from kitchen tiles, but showed no improvement over **(54)**. Thus, the benzoxazolium and benzothiazolium salts tested are not useful for the removal of these types of stains.

This is probably because the rate of decomposition of the mediator is too fast for sufficient oxidation of the stains to take place.

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[1] J. Thornton, "The Product is the Poison: The Case for a Chlorine Phase-Out" (Washington, D.C.: Greenpeace, 1991).

[2] U.S. EPA, President Clinton's Clean Water Initiative, February 1994.

[3] Report of the Carcinogenesis Bioassay of Chloroform, NTIS PB264018/AS, National Cancer Institute, 1976.

[4] R.D. Morris, A. Audet, I.F. Angelillo, T. C. Chalmers, and F. Mosteller, "Chlorination, Chlorination by-products, and cancer: A meta-analysis". *American Journal of Public Health*, 1992, **82**, (7), 955-977.

[5] USEPA National Primary Drinking Water Regulations Part 141.

[6] Science & Technology Report, Unilever Reserch Ltd., Port Sunlight (*confidential*).

Chapter 7

Experimental Section

7.1 Instrumentation and Experimental Techniques

All reagents were used as supplied.

Flash column chromatography was performed using Merck® silica gel 60 (230-400 mesh); when necessary compressed air was used to pressurise the column. Thin layer chromatography (TLC) was carried out on Merck® aluminium plates coated with 0.25 mm layer of silica gel containing a fluorescence indicator; UV inactive compounds were visualised by exposure to iodine.

High performance liquid chromatography (HPLC) was carried out using a Dynamax® SD-200 pump and a Dynamax® UV-1 detector. Columns used were a Rainin® C18 and a HiChrom® C18; both had the same manufacturer specifications: 4.6 mm internal diameter, 5 μm particle size, 25 cm in length, pore size 60 Å. The solvents used were either methanol/ water (8:2) or acetonitrile/ water (8:2); the detector was set at 240 nm and the flow rate was 0.5 or 1.0 $ml.min^{-1}$.

Mass spectra were recorded on a Fisons Trio® 1000 spectrophotometer (EI) and a VG7070E spectrometer. For FAB spectra 3-nitrobenzylalcohol was used as the matrix and xenon as the fast atom.

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian® Gemini 300 (300 MHz) spectrometer. Deuteriochloroform was used as the solvent with tetramethylsilane as internal standard unless otherwise stated. Spectra are recorded on the δ scale and signals are given in the form (number of protons; multiplicity; assignment) and measured in parts per million (ppm) downfield from TMS.

Infrared spectra were recorded in the range 4000-600 cm^{-1} using Perkin-Elmer 883 infrared spectrophotometer with polystyrene as a reference. Spectra of oils were taken neat; spectra of solids were taken as nujol mulls using sodium chloride cells.

Microanalyses were performed using a Carlo Erba® elemental analyser at the University of Liverpool, Department of Chemistry, Microanalytical laboratory.

Melting points were recorded on a Gallenkamp® melting point apparatus and are uncorrected for pressure.

All yields given refer to analytically pure compounds unless otherwise stated.

7.2 General Procedures For The Oxidation Of Sulfides

All glassware used for the oxidation reactions was cleaned using disodium EDTA solution to sequester any metal ions which may catalyse decomposition of hydrogen peroxide.

Initial assessment of mediators

Thioanisole (0.20 g; 1.61 mmol; 1.00 eq) was added to a suspension of sodium percarbonate (0.67 g; 4.27 mmol; $^{8}/_{3}$ eq;) in 6.0 cm^3 methanol containing biphenyl as an internal standard. To this suspension was added mediator (0.40 mmol; $^{1}/_{4}$ eq) and the reaction vessel was placed in a waterbath at 25°C and the reaction mixture stirred for 48 hours.

Reactions carried out at 40°C used conditions identical to those described above.

The reactions carried out with increased initial concentrations of the reactants were carried out as described above, apart from the increase in the relevant component. For the cases of increased hydrogen peroxide concentration it was necessary to add aqueous hydrogen peroxide and sodium carbonate as shown:

Thioanisole (0.20 g; 1.61 mmol; 1.00 eq) was added to a suspension of sodium percarbonate (0.67 g; 4.27 mmol; $^{8}/_{3}$ eq;) and sodium carbonate (0.17 g; 1.60 mmol; 0.99 eq;) in 6.0 cm^3 methanol containing biphenyl as an internal standard. To this suspension was added hydrogen peroxide (30 % (w/v); 1.76 mmol; 1.09 eq) and mediator (0.40 mmol; $^{1}/_{4}$ eq). The reaction vessel was placed in a waterbath at 25°C and the reaction mixture stirred for 48 hours.

Determination of peroxide concentration

The solution of peroxide under investigation was added to an acidified sodium iodide solution to liberate iodine. Whilst stirring vigorously the solution was titrated against standard sodium thiosulfate solution. When the end-point was near (pale yellow colour) starch indicator was added and the solution turned blue-black in colour; when the solution became colourless this indicated complete reduction of iodine to iodide.

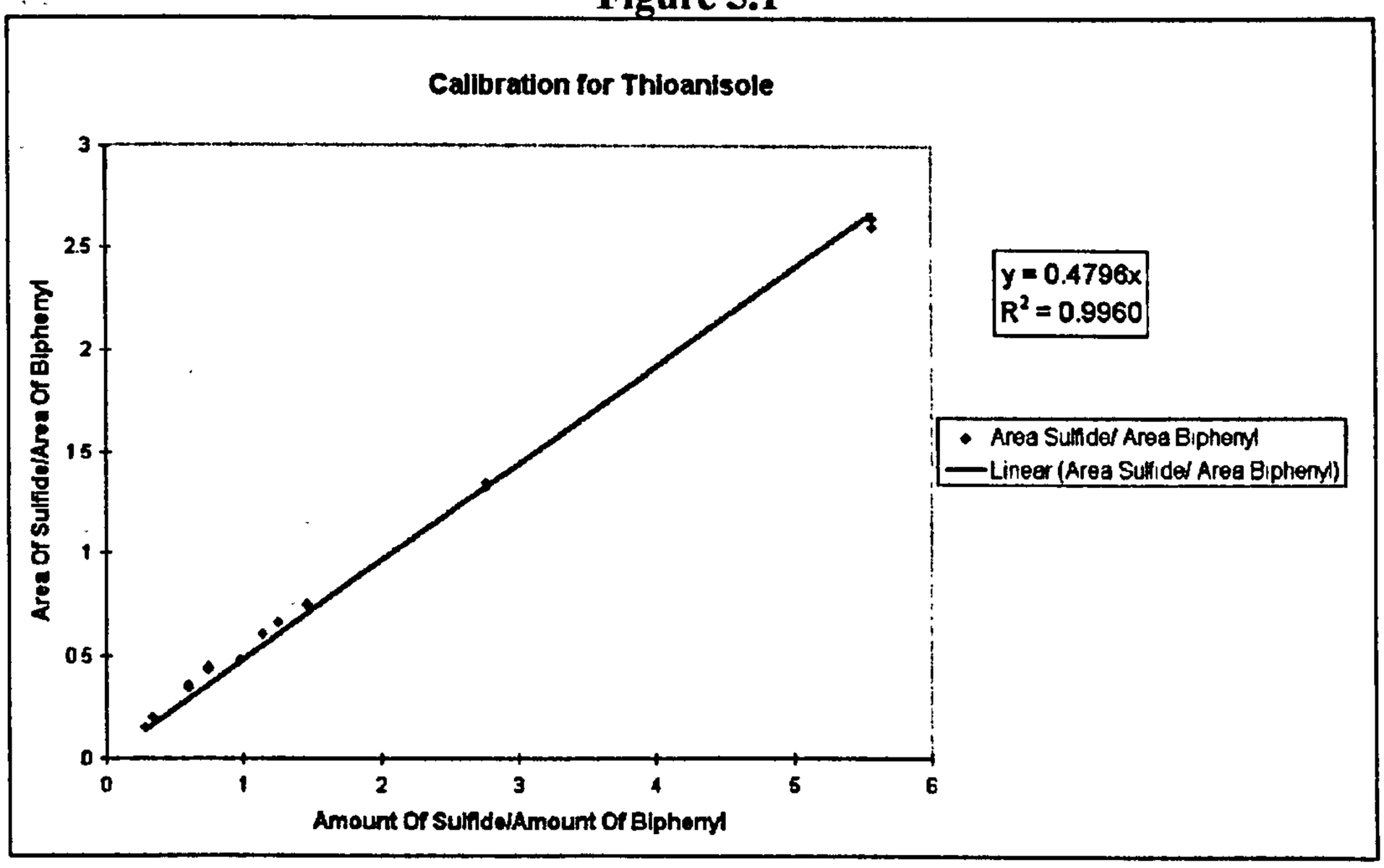
7.3 HPLC analysis

Aliquots (0.2 cm^3) from the reaction under investigation (taken at 0, 10, 20, 30, 40, 50, 60, 120, 240, 360, 1440, 2880 minutes) were added to an aqueous solution of sodium sulfite (5-10 mg) to quench the oxidant. This mixture was diluted (with methanol or acetonitrile) and then placed in an ultrasonic bath until homogenous. The sample was then diluted to the appropriate concentration for HPLC analysis. Biphenyl was present in the reaction mixture as an internal standard.

Instrument calibration

The HPLC equipment was calibrated by making up solutions containing a range of different concentrations of biphenyl and the appropriate sulfide (in the case of thioanisole the equipment was also calibrated for phenyl methyl sulfoxide). These solutions were then analysed and a calibration chart was constructed by plotting the area of sulfide/ the area of biphenyl against the concentration of sulfide/ the concentration of biphenyl (**Figure 5.1**).

Figure 5.1



From the calibration chart, the unknown concentration of sulfide can be calculated from the ratio of the area of the sulfide to the area of the internal standard, if one knows the concentration of the internal standard in the sample:

[sulfide] = ([biphenyl]/gradient) x (area sulfide/area biphenyl)

7.4 Preparation of sulfide reactants and sulfoxide products

Methyl-(4-trifluoromethyl-phenyl) sulfide[1]

Dimethyl sulfate (2.83 g; 22.44 mmol; 2.0 eq) was added dropwise (over one hour) to 4-trifluoromethylthiophenol (2.00 g; 11.23 mmol; 1.00 eq) in 10 % sodium hydroxide solution (7.0 cm^3). After one hour a further portion of 10 % sodium hydroxide solution (3.0 cm^3) was added and the mixture was stirred for another hour. The product was extracted into diethyl ether, dried (magnesium sulfate) and the solvent removed to yield an off-white solid (1.99 g; 92 %).

mp = 35-37°C; Lit.[2] = 37°C

MS (EI) m/z = 192 (M^+); $C_8H_7F_3S$ requires: 192.02.

MS (Acc) m/z = 192.02244; $C_8H_7F_3S$ requires: 192.02206.

^{1}H-NMR (300MHz, $CDCl_3$): δ, 2.51 (3H, s, CH_3), 7.28-7.34 (2H, d, Ar-H), 7.50-7.56 (2H, d, Ar-H).

General Procedure For Sulfoxide Preparation[3]**.**

Sulfide (24.62 mmol; 1.00 eq) in methanol (50 cm^3) was added dropwise to a stirring solution of sodium periodate (5.79 g; 27.07 mmol; 1.1 eq) in water (70 cm^3) cooled to 0°C. After the sulfide was consumed (TLC) the reaction mixture was extracted into DCM, dried (magnesium sulfate) and the solvent removed to yield the product.

Phenyl methyl sulfoxide

mp = 29°C; Lit.[3] = 29-30°C

Found: C, 59.96; H, 5.75. C_7H_8OS requires: C, 59.97; H, 5.75.

MS (EI) m/z = 140 (M^+); C_7H_8SO requires: 140.20.

^{1}H-NMR (300MHz, $CDCl_3$): δ, 2.76 (3H, s, CH_3), 7.50-7.58 (3H, m, Ar-H), 7.63-7.69 (2H, m, Ar-H).

Retention time = 6.3 mins (90 % MeCN $_{(aq)}$; 0.5 $mL.min^{-1}$); 5.9 mins (80 % MeCN $_{(aq)}$; 0.5 $mL.min^{-1}$).

Methyl-(4-trifluoromethyl-phenyl) sulfoxide

Isolated as a colourless solid after recystallisation from hexane (0.70 g; 41 %).

mp = 42-43°C. Lit.[4] = 39-41°C

MS (EI) m/z = 208 (M^+); $C_8H_7F_3OS$ requires: 208.02.

MS (Acc) m/z = 208.01732; $C_8H_7F_3OS$ requires: 208.01698.

^{1}H-NMR (300MHz, $CDCl_3$): δ, 2.70 (3H, s, CH_3), 7.70 (4H, s, Ar-H).

^{13}C-NMR (400MHz, $CDCl_3$): δ, 43.97 (s, CH_3), 123.55 (q, *J* 273, CF_3), 124.07 (s, Ar-C), 126.42 (s, Ar-C), 132.77 (q, *J* 33.1, Ar-C-CF_3), 150.30 (s, Ar-C-SO).

IR: ν_{max}: 3486 (m), 3046 (m), 3002 (m), 2920 (m), 1607 (s), 1333 (s), 1169 (s), 1138 (s), 1058, (s), 1013 (s), 956 (s), 838 (s), 730 (w), 699 (s), 676 (m).

Methyl-(4-bromo-phenyl) sulfoxide

Isolated as a colourless solid after flash column chromatography using hexane as eluent (4.86 g; 90 %).

mp = 79°C; Lit.[5] = 84-86°C.

Found: C, 38.59; H, 3.21. C_7H_7BrOS requires: C, 38.54; H, 3.24.

MS (EI) m/z = 220, 218 (M^+); C_7H_7BrOS requires: 220, 218.

^{1}H-NMR (300MHz, $CDCl_3$): δ, 2.70 (3H, s, CH_3), 7.51-7.58 (2H, d, Ar-H), 7.63-7.70 (2H, d, Ar-H).

Methyl-(4-methoxyphenyl) sulfoxide

Isolated as a colourless solid after recystallisation from hexane.

mp = 39.5-41.5°C; Lit.[5] = 41-43°C.

Found: C, 56.29; H, 5.98. $C_8H_{10}O_2S$ requires: C, 56.45; H, 5.92.

MS (EI) m/z = 170 (M^+, 20 %); $C_8H_{10}O_2S$ requires: 170.23.

^{1}H-NMR (300MHz, $CDCl_3$): δ, 2.70 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 7.03 (2H, d, Ar-H), 7.60 (2H, d, Ar-H).

Methyl-(4-nitrophenyl) sulfoxide

Isolated as a colourless solid after recystallisation from hexane.

mp = 151°C; Lit.[6] = 151-152°C

Found: C, 45.37; H, 3.76; N, 7.54. $C_7H_7NO_3S$ requires: C, 45.40; H, 3.81; N, 7.57.

MS (EI) m/z = 185 (M^+); $C_7H_7NO_3S$ requires: 185.20.

^{1}H-NMR (300MHz, $CDCl_3$): δ, 2.81 (3H, s, CH_3), 7.86 (2H, d, Ar-H), 8.40 (2H, d, Ar-H).

Methyl-(*p*-tolyl) sulfoxide

Isolated as a white solid after flash column chromatography (1.16 g; 85 %).

mp = 40.5-43°C; Lit[7]. = 41-43°C[8].

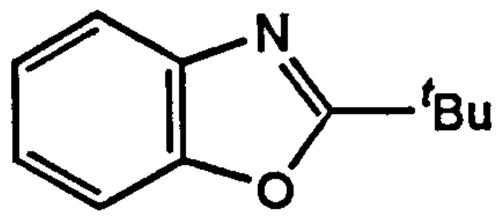
Found: C, 62.37; H, 6.55. $C_8H_{10}OS$ requires: C, 62.30; H, 6.54.

MS (EI) m/z = 154; $C_8H_{10}OS$ requires: 154.05.

^{1}H-NMR (300MHz, $CDCl_3$): δ, 2.42 (3H, s, CH_3-Ar), 2.70 (3H, s, CH_3), 7.33 (2H, d, Ar-H), 7.54 (2H, d, Ar-H).

7.5 Preparation of *O*-transfer mediators and their precursors

2-*tert*-Butylbenzoxazole (30)[9]



(30)

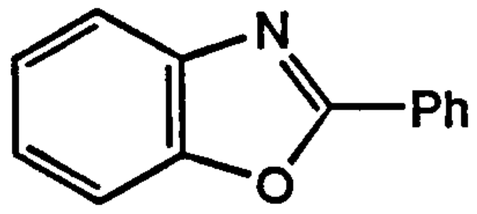
o-Aminophenol (5.00 g; 45.82 mmol; 1.00 eq) was dissolved in the minimum amount of chloroform (or acetonitrile) and cooled below 0°C using an ice/ salt bath. Pivaloyl chloride (8.29 g; 68.75 mmol; 1.50 eq) was added dropwise and the mixture was stirred for 30 minutes. The ice bath was removed and the mixture stirred for a further 30 minutes. Solvent removal yielded a white solid to which phosphorous pentoxide (3.25 g; 22.89 mmol; 0.50 eq) was added. The solids were heated until they fused (approximately half an hour at 200°C). After cooling, distilled water was carefully added and then sodium carbonate solution. This mixture was extracted into hexane, dried (magnesium sulfate) and the solvent was removed. After passage through a short column of silica, a red oil was obtained (3.6 g; 45 %).

Found: C, 75.32; H, 7.54; N, 8.03. $C_{11}H_{13}NO$ requires: C, 75.39; H, 7.48; N, 8.00.

MS (EI) m/z = 175 (M^+); $C_{11}H_{13}NO$ requires:175.23.

^{1}H NMR (300MHz, $CDCl_3$): δ, 1.50 (9H, s, $C(CH_3)_3$), 7.30 (2H, m, Ar-H),7.50 (1H, m, Ar-H), 7.70 (1H, m, Ar-H).

2-Phenylbenzoxazole (31)[10]



(31)

o-Aminophenol (10.00 g; 91.63 mmol; 1.00 eq) and boric acid (5.70 g; 92.19 mmol; 1.01 eq) were dissolved in *tert*-butylbenzene (150 cm^3) and benzoyl chloride (12.9 g; 91.77 mmol; 1.00 eq) was added to the solution. After the addition, the mixture was heated at 130°C for 19.5 hours. Then toluene was added to the mixture and it was filtered to give a red solution which was concentrated and the product was purified by flash column chromatography using toluene as eluent (11.1 g; 62 %).

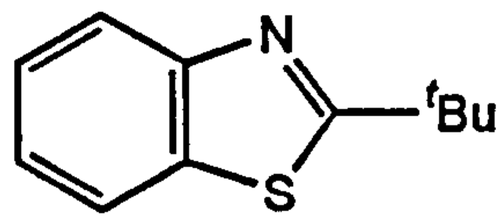
mp = 104°C; Lit.[11] = 102-4°C.

Found: C, 80.01; H, 4.68; N, 7.15. $C_{13}H_9NO$ requires: C, 79.98; H, 4.65; N, 7.17.

MS (EI) m/z = 195(M^+); $C_{13}H_9NO$ requires: 195.22.

^{1}H NMR (300MHz, $CDCl_3$): δ, 7.30 (m, Ar-**H**) 7.50 (m, Ar-**H**), 7.80 (m, Ar-**H**), 8.3 (m, Ar-**H**)

2-*tert*-Butylbenzothiazole (33)[10]



(33)

o-Aminothiophenol (10.00 g; 79.88 mmol; 1.00 eq) and boric acid (4.94 g; 79.90 mmol; 1.00 eq) were dissolved in *tert*-butylbenzene (150 cm^3) and pivaloyl chloride (11.56 g; 95.87 mmol; 1.20 eq) was added to the solution. After the addition, the mixture was heated at 150°C for 72 hours. After filtration to separate the product from *N*-(2-2',2'-dimethylpropylmercapto-phenyl)-2',2'-dimethylpropionamide **(32)** (1.20 g; 5.1 %), the product was isolated by column chromatography to give a yellow oil (3.6 g; 24 %).

Found: C, 68.84; H, 6.88; N, 7.36. $C_{11}H_{13}NS$ requires: C, 69.08; H, 6.86; N, 7.33.

MS (EI) m/z = 191 (M^+); $C_{11}H_{13}NS$ requires: 191.29.

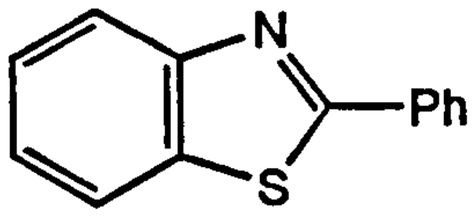
^{1}H NMR (300MHz, $CDCl_3$): δ, 1.49 (9H, s, $C(CH_3)_3$), 7.22-7.43 (1H, t, Ar-**H**),7.45 (1H, t, Ar-**H**), 7.75-7.82 (1H, d, Ar-**H**), 7.96-8.30 (1H, d, Ar-**H**).

_N_-(2-2',2'-Dimethylpropylmercapto-phenyl)-2',2'-dimethylpropionamide (32)

MS (EI) m/z = 293 (M^+); $C_{16}H_{23}NO_2S$ requires: 293.14.

^{1}H NMR (300MHz, $CDCl_3$): δ, 1.28 (9H, s, $C(CH_3)_3$), 1.35 (9H, s, $C(CH_3)_3$), 7.10 (1H, t, Ar-H), 7.36 (1H, d, Ar-H), 7.44 (1H, t, Ar-H), 8.38 (1H, d, Ar-H).

2-Phenylbenzothiazole (34)[9]



(34)

o-Aminothiophenol (4.80 g; 38.3 mmol; 1.00 eq) was dissolved in the minimum amount of chloroform and cooled using an ice/ salt bath. Benzoyl chloride (25.76 g; 183.25 mmol; 4.78 eq) was added slowly to the stirring solution. After the addition, the ice bath was removed and the mixture stirred for one hour. Then the chloroform was removed by distillation and the residue dissolved in aqueous sodium carbonate solution and boiled for 30 minutes. Extraction into ether, drying and removal of solvent yielded 2-phenylbenzothiazole as a yellow solid (6.9 g; 85 %).

mp = 116°C; Lit.[12] = 115-7°C.

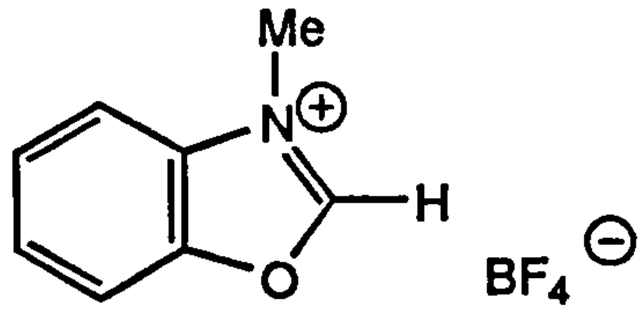
Found C, 74.21; H, 4.35, N, 6.44. $C_{13}H_9NS$ requires: C, 73.90; H, 4.29; N, 6.63.

MS (EI) m/z = 211 (M^+); $C_{13}H_9NS$ requires: 211.28.

^{1}H NMR (300MHz, $CDCl_3$): δ, 7.40 (2H, m, Ar-H), 7.50 (4H, m, Ar-H), 7.90 (1H, d, Ar-H), 8.10 (2H, m, Ar-H).

Preparation of O-transfer mediators

3-Methylbenzoxazolium tetrafluoroborate (35)[14]



(35)

Benzoxazole (1.00 g; 8.39 mmol; 1.00 eq) was dissolved in DCM (10 cm^3) and trimethyloxonium tetrafluoroborate (1.37 g; 9.26 mmol; 1.10 eq) added. After 24 hours, diethyl ether was added to the mixture and the resulting precipitate was

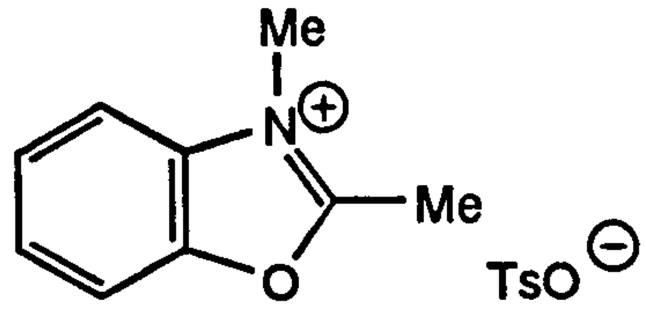
collected by filtration and washed with more ether (1.50 g; 81 %).

mp = 147-9°C (decomp.)

MS (FAB, Acc) m/z = 134.06102 (M^+); $C_8H_8NO^+$ requires: 134.06059.

^{1}H NMR (300MHz, D^6 acetone): δ, 4.43 (3H, s, N^+CH_3), 7.85-7.88 (2H, m, Ar-H), 8.12-8.30 (2H,m, Ar-H), 10.25 (1H, s, N=CH).

2,3-Dimethylbenzoxazolium tosylate (47)[13]



(47)

Methyl *p*-toluenesulfonate (1.94 g; 10.42 mmol; 1.00 eq) and 2-methylbenzoxazole (1.39 g; 10.44 mmol; 1.00 eq) were dissolved in acetonitrile (2 cm^3) and stirred overnight until a precipitate appeared. After the addition of diethyl ether, the product, a white solid, was removed by filtration and washed with more ether. The solvent was removed from the filtrate and the remaining liquid stirred until further precipitation occurred (2.0 g; 60 %).

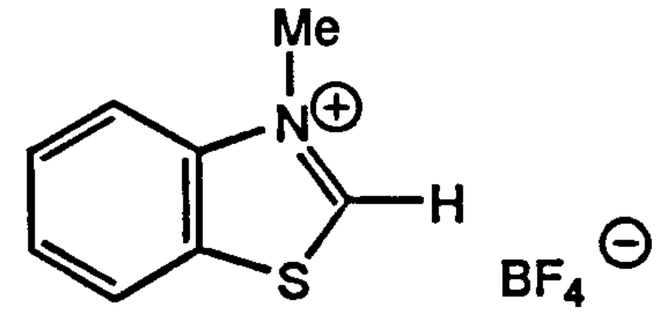
mp = 159°C; Lit.[19] = 164°C.

Found C, 59.98; H, 5.34; N, 4.43. $C_{16}H_{17}NO_4S$ requires: C, 60.17; H, 5.37; N, 4.39.

MS (FAB) m/z = 148 (M^+), 467 $(M_2X)^+$; $C_9H_{10}NO^+$ requires 148.08, requires: 467.

^{1}H NMR (300MHz, $CDCl_3$): δ, 2.30 (3H, s, Ar-CH_3), 3.15 (3H, s, CH_3), 4.25 (3H, s, N^+CH_3), 7.00 (2H, d, Ar-H), 7.50 (2H, d, Ar-H), 7.55-7.80 (4H, m, Ar-H).

3-Methylbenzothiazolium tetrafluoroborate (38)[14]



(38)

Benzothiazole (2.00 g; 14.79 mmol; 1.00 eq) was dissolved in acetonitrile (4 cm^3) and trimethyloxonium tetrafluoroborate (2.41 g; 16.23 mmol; 1.10 eq) added. After 24 hours, diethyl ether was added to the mixture and the resulting precipitate was

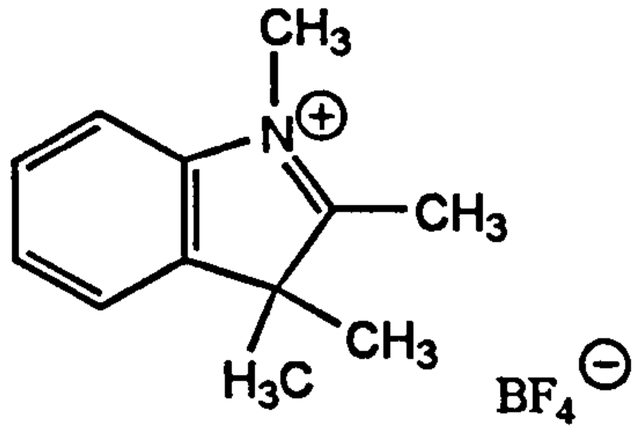
collected by filtration and washed with more ether (3.50 g; 99 %).

mp = 119-120°C; Lit.[14] = 118.5-119.5°C.

MS (FAB, Acc) m/z = 150.03791 (M^+); $C_8H_8NS^+$ requires: 150.03775.

^{1}H NMR (300MHz, D^6 acetone): δ, 4.60 (3H, s, N^+CH_3), 7.80-7.88 (1H, t, Ar-H), 7.90-7.98 (1H, t, Ar-H), 8.26-8.32 (1H,d, Ar-H), 8.37-8.45 (1H,d, Ar-H), 10.45 (1H, s, N=CH).

1,2,3,3-Tetramethylindoleninium tetrafluoroborate (44)



(44)

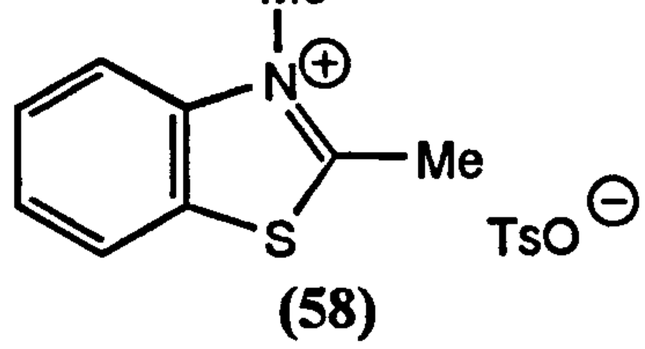
2,3,3-Trimethyl indolenine (1.00 g; 6.28 mmol; 1.00 eq) was dissolved in acetonitrile (10 cm^3) and trimethyloxonium tetrafluoroborate (1.02 g; 6.90 mmol; 1.10 eq) added. After 24 hours, diethyl ether was added to the mixture and the resulting precipitate was collected by filtration and washed with more ether (1.60 g; 89 %).

mp = 197°C (decomp.); Lit.[15] = 201-3°C

MS (FAB, Acc) m/z = 174.12830 (M^+); $C_{12}H_{16}N^+$ requires: 174.12828.

^{1}H NMR (300MHz, D_2O): δ, 1.50 (6H, s, 3-CH_3), 3.90 (3H, s, N^+CH_3), 7.60 (2H, m, Ar-H), 7.70 (2H, m, Ar-H).

2,3-Dimethylbenzothiazolium tosylate (58)



(58)

Methyl *p*-toluenesulfonate (3.09 g 16.6 mmol; 1.23 eq) was dissolved in 2-methylbenzothiazole (2.01 g; 13.5 mmol; 1.00 eq) and stirred for 24 hours. After the addition of diethyl ether, the resulting pale yellow precipitate was removed by

filtration and washed with diethyl ether. The solvent was removed from the washings and the mixture was stirred for several days yielding another crop of yellow crystals (total yield: 3.46 g; 77 %).

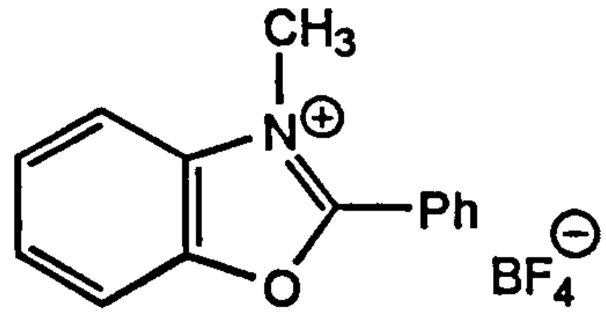
mp = 177-9°C (decomp.); Lit.[16] = 186°C.

Found C, 57.16; H, 5.09; N, 4.16. $C_{16}H_{17}NO_3S_2$ requires: C, 57.30; H, 5.11; N, 4.18.

MS (EI) m/z = 164 (M^+); $C_9H_{10}NS^+$ requires: 164.06.

^{1}H NMR (300MHz, D_2O): 2.25 (3H, s, Ar-CH_3), 3.10 (3H, s, CH_3), 4.10 (3H, s, N^+CH_3), 7.18 (2H, d, Ar-H), 7.55 (2H, d, Ar-H), 7.76 (1H, t, Ar-H), 7.85 (1H, t, Ar-H), 8.00 (1H, d, Ar-H), 8.13 (1H, d, Ar-H).

2-Phenyl-3-methylbenzoxazolium tetrafluoroborate (36)



(36)

Trimethyloxonium tetrafluoroborate (1.67 g; 11.29 mmol; 1.10 eq) was added to a solution of 2-phenylbenzoxazole (2.00 g; 10.24 mmol; 1.00 eq) in dichloromethane (10 cm^3) and stirred overnight. Removal of the solvent yielded a crop of white crystals which were recrystallised by dissolving in the minimum amount of hot acetone, filtering and slowly adding diethyl ether to the cooled solution (2.68 g; 88 %).

mp = 168-170°C

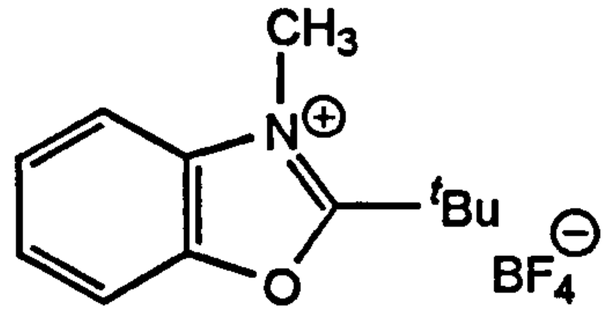
MS (Acc) m/z = 210.09194 (M^+); $C_{14}H_{12}NO^+$ requires: 210.09189.

^{1}H NMR (300MHz, D^6 acetone): δ, 4.60 (3H, s, N^+CH_3), 7.80-8.10 (5H, m, Ar-H), 8.20 (1H, m, Ar-H), 8.30 (1H, m, Ar-H), 8.40 (2H, m, Ar-H).

^{1}H NMR (300MHz, D^6 DMSO): 3.20 (3H, s, N^+CH_3), 6.60 (1H, t, Ar-H), 6.8 (1H, d, Ar-H), 7.00 (2H, m, Ar-H), 7.10-7.30 (5H, m, Ar-H).

^{1}H NMR (300MHz, CD_3CN): 4.27 (3H, s, N^+CH_3), 7.78-7.89 (4H, m, Ar-H), 7.91-7.98 (1H, m, Ar-H), 7.99-8.06 (2H, m, Ar-H), 8.15-8.23 (2H, m, Ar-H).

2-*tert*-Butyl-3-methylbenzoxazolium tetrafluoroborate (37)



(37)

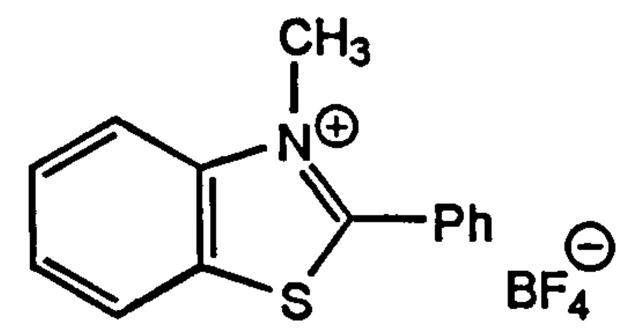
Trimethyloxonium tetrafluoroborate (1.01 g; 6.83 mmol; 1.20 eq) was added to a solution of 2-*tert*-butylbenzoxazole (1.00 g; 5.71 mmol; 1.00 eq) in dichloromethane and stirred overnight. Removal of solvent yielded a crop of white crystals, which were recrystallised by dissolving in the minimum amount of hot acetone, filtering and slowly adding diethyl ether to the cooled solution (1.47 g, 93 %).

mp = 163-4°C

MS (FAB; Acc) m/z = 190.12282 (M^+); $C_{12}H_{16}NO^+$ requires: 190.12319.

^{1}H NMR (300MHz, CD_3OD): δ, 1.75 (9H, s, $C(CH_3)_3$), 4.30 (3H, s, N^+CH_3), 7.54-7.58 (1H, m), 7.61-7.65 (1H, m), 7.78-7.82 (1H, m), 7.97-8.04 (1H, m).

2-Phenyl-3-methylbenzothiazolium tetrafluoroborate (39)



(39)

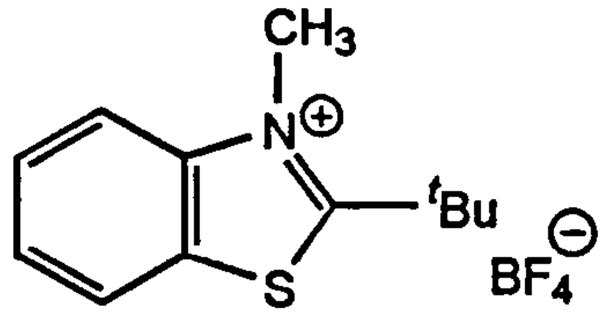
Trimethyloxonium tetrafluoroborate (0.77 g; 5.21 mmol; 1.10 eq) was added to a solution of 2-phenylbenzothiazole (1.00 g; 4.73 mmol; 1.00 eq) in dichloromethane (20 cm^3) and stirred overnight. Removal of solvent yielded a crop of white crystals, which were stirred with diethyl ether overnight. Filtration yielded the required compound (1.23 g, 83 %).

mp = 197-9°C.

MS (Acc) m/z = 226.06921 (M^+). $C_{14}H_{12}NS^+$ requires: 226.06905.

^{1}H NMR (300MHz, D^6 acetone): δ, 4.50 (3H, s, N^+CH_3), 7.80-8.10 (5H, m, Ar-H), 8.50 (1H, d, Ar-H), 8.60 (1H, d, Ar-H).

2-*tert*-Butyl-3-methylbenzothiazolium tetrafluoroborate (40)[17]



(40)

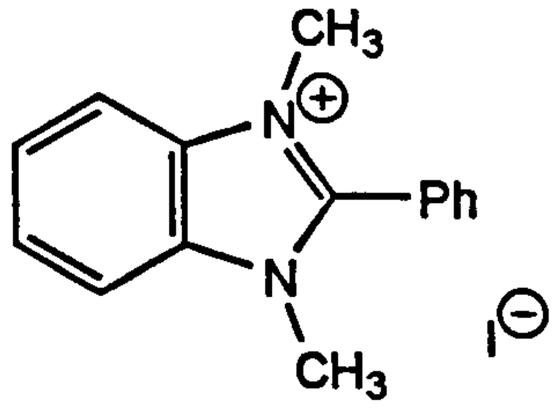
Trimethyloxonium tetrafluoroborate (0.67 g; 4.53 mmol; 1.01 eq) was added to a solution of 2-*tert*-butylbenzothiazole (0.86 g; 4.50 mmol; 1.00 eq) in dichloromethane (10 cm^3) and stirred overnight. Removal of solvent yielded a crop of white crystals, which were stirred with diethyl ether overnight. Filtration yielded the title compound (1.24 g, 94 %).

mp = 218-9°C; Lit.[17] = 218-220°C.

MS (FAB; Acc) m/z = 206.10045 (M^+); $C_{12}H_{16}NS^+$ requires: 206.10035.

^{1}H NMR (300MHz, CD_3OD):δ 1.80 (9H, s, $C(CH_3)_3$), 4.50 (3H, s, N^+-CH_3), 7.80 (1H, t, Ar-H), 7.95 (1H, t, Ar-H), 8.25 (1H, d, Ar-H), 8.35 (1H, d, Ar-H).

1, 3-Dimethyl-2-phenylbenzimidazolium iodide



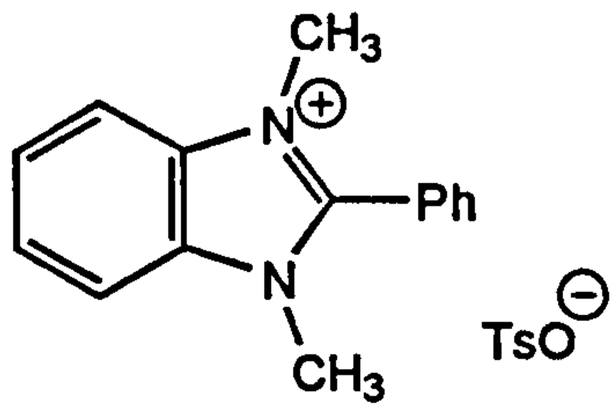
To 2-phenylbenzimidazole (1.00 g; 5.15 mmol; 1.00 eq) and sodium methoxide (0.42 g; 7.77 mmol; 1.50 eq) was added methanol (10 cm^3) and methyl iodide (2.20 g; 15.50 mmol; 3.00 eq). The mixture was refluxed for 4 hours. After cooling, more methanol was added and the solution was filtered. The addition of diethyl ether precipitated the iodide salt.

Found C, 51.28; H, 4.30, N, 7.97. $C_{15}H_{15}N_2I$ requires: C, 51.45; H, 4.32; N, 8.00.

MS (EI) m/z = 223 (M^+); $C_{15}H_{15}N_2I$ requires: 340; $C_{15}H_{15}N_2^+$ requires: 223

^{1}H NMR (300MHz, CD_3OD): δ, 3.95 (6H, s, 2xCH_3), 7.75-7.90 (6H, m, Ar-H), 7.95-8.05 (3H, m, Ar-H).

1, 3-Dimethyl-2-phenylbenzimidazolium tosylate (43)



(43)

Silver tosylate (0.50 g; 1.79 mmol; 1.42 eq) dissolved in acetonitrile (25 cm^3) was treated with 1, 3-dimethyl-2-phenylbenzimidazolium iodide (0.44 g; 1.26 mmol; 1.00 eq) in 20 cm^3 of acetonitrile and the mixture was stirred for 18 hours. A yellow precipitate was formed and was separated from the colourless solution by filtration. The title compound was isolated by removal of solvent from the filtrate (0.23 g; 51 %); the solid tested negative for iodide (hydrogen peroxide) and for silver ions (sodium thiosulfate).

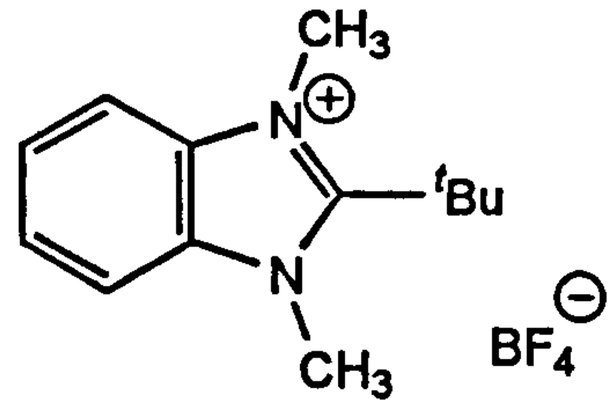
mp = 229-231°C.

Found C, 67.12; H, 5.62; N, 7.08. $C_{22}H_{22}N_2O_3S$ requires: C, 66.98; H, 5.62; N, 7.10.

MS (EI; Acc) m/z = 223.12402 (M^+); $C_{15}H_{15}N_2^+$ requires: 223.12352.

^1H NMR (300MHz, $CDCl_3$): δ, 2.25 (3H, s, Ar-CH_3), 4.00 (6H, s, 2xCH_3), 6.96 (2H, d, Ar-H), 7.39 (2H, d, Ar-H), 7.60-7.80 (6H, m, Ar-H), 7.92-8.00 (3H, m, Ar-H).

1, 3-Dimethyl-2-*tert*-butylbenzimidazolium tetrafluoroborate (42)



(42)

To 2-*tert*-butylbenzimidazole (5.50 g; 31.56 mmol; 1.00 eq) and sodium methoxide (2.50 g; 48.06 mmol; 1.52 eq) was added methanol (35 cm^3) and methyl iodide (13.50 g; 5.9 cm^3; 95.11 mmol; 3.01 eq). The mixture was refluxed for 48 hours. After cooling diethyl ether was added, which precipitated some 1, 3-dimethyl-2-*t*-butylbenzimidazolium iodide, which was recovered by filtration (3.2 g; 31 %;9.69 mmol). The solvent was removed from the filtrate to yield 1-methyl-2-*tert*-

butylbenzimidazole (2.2 g; 37 %; 11.69 mmol) which was mixed with Meerwein's reagent and dissolved in acetonitrile (50 mL). After stirring at room temperature overnight some solvent was removed and diethyl ether added to precipitate the iminium salt, which was recrystallised by dissolving in the minimum amount of acetonitrile, filtering and slowly adding diethyl ether to the filtrate (0.72 g, 2.48 mmol; 21 %).

1, 3-Dimethyl-2-*t*-butylbenzimidazolium iodide

Found C, 47.40, H, 5.78, N, 8.45. $C_{15}H_{15}N_2I$ requires: C, 47.29, H, 5.80, N, 8.48.

MS (EI) m/z = 203 (M^+); $C_{13}H_{19}N_2^+$ requires: 203.15.

^{1}H-NMR (300MHz, CD_3OD): δ, 1.82 (9H, s, $C(CH_3)_3$), 4.28 (6H, s, 2x $N^{\delta+}CH_3$), 7.67-7.70 (2H, m, Ar-**H**), 7.90-7.93 (2H, m, Ar-**H**).

1-Methyl-2-*t*-butylbenzimidazole

MS (EI) m/z =188 (M^+); $C_{12}H_{16}N_2$ requires: 188.13.

^{1}H-NMR (300MHz, D^6 acetone): δ, 1.71 (9H, s, $C(CH_3)_3$), 4.23 (3H, s, N-CH_3), 7.38-7.52 (2H, quint, Ar-**H**), 7.76-7.86 (1H, d, Ar-**H**), 8.10-8.18 (1H, d, Ar-**H**).**1, 3-Dimethyl-2-*tert*-butylbenzimidazolium tosylate**

Silver tosylate (0.79 g; 2.83 mmol; 1.51 eq), dissolved in acetonitrile (5 cm^3) was added to 1, 3-dimethyl-2-*tert*-butylbenzimidazolium iodide (0.62 g; 1.88 mmol; 1.00 eq) in 20 cm^3 of actetonitrile. A yellow precipitate was formed immediately and was separated from the colourless solution by filtration. The title compound was isolated by removal of solvent from the filtrate (0.60 g; 86 %); the solid tested negative for iodide (hydrogen peroxide) and for silver (sodium thiosulfate).

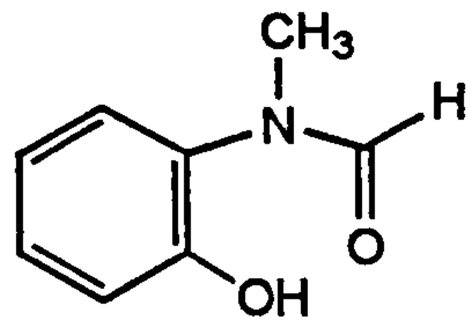
Found C: 60.91, H: 7.21, N: 7.15. $C_{20}H_{26}N_2O_3S$ requires: C: 64.14, H: 7.00, N: 7.48. $C_{20}H_{26}N_2O_3S.H_2O$ requires: C: 61.20, H: 7.19, N: 7.14.

MS (EI) m/z = 203 (M^+); $C_{13}H_{19}N_2^+$ requires: 203.

^{1}H-NMR (300MHz, $CDCl_3$): δ, 1.76 (9H, s, $C(CH_3)_3$), 2.27 (3H, s, $ArCH_3$), 4.22 (6H, s, 2x $N^{\delta+}CH_3$), 6.93-7.20 (2H, d, Ar-**H**), 7.48-7.60 (4H, m, Ar-**H**), 7.68-7.76 (2H, m, Ar-**H**).

7.6 Products arising from the decomposition of the mediators

N-(2-Hydroxyphenyl)-*N*-methyl-formamide (48)



(48)

3-Methylbenzoxazolium tetrafluoroborate (0.1058 g; 0.479 mmol) was dissolved in water (4.0 mL) and the solution extracted with DCM. After drying (magnesium sulfate) and solvent removal a white solid remained.

mp = 98°C; Lit.[18] = 103-107°C.

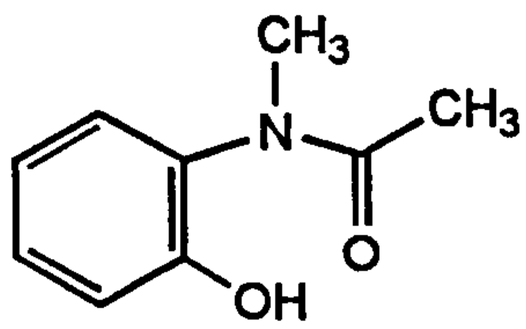
Found: C, 63.60; H, 6.06; N, 9.25. $C_8H_9NO_2$ requires: C, 63.57; H, 6.00; N, 9.27.

MS (EI) m/z = 151 (M^+); $C_8H_9NO_2$ requires 151.06

^{1}H NMR (300MHz, $CDCl_3$): δ, 3.24 (3H, s, CH_3-N), 6.86-6.93 (1H, t, Ar-**H**), 7.01-7.05 (1H, d, Ar-**H**), 7.05-7.10 (1H, d, Ar-**H**), 7.18-7.25 (1H, t, Ar-**H**), 8.20 (1H, s, **CHO**).

Retention time = 4.9 mins (90 % MeCN $_{(aq)}$; 0.5 mL.min^{-1}).

N-(2-Hydroxyphenyl)-*N*-methyl-acetamide (49)[19]



(49)

2,3-Dimethylbenzoxazolium tosylate (0.0398 g; 0.125 mmol) was dissolved in water (4.0 mL) and left to stand for seven days. A white precipitate was formed which was removed by filtration to give the title compound.

mp = 146°C (decomp.); Lit.[19] = 149-150°C.

Found: C, 65.34; H, 6.70; N, 8.45. $C_9H_{11}NO_2$ requires: C, 65.42; H, 6.72; N, 8.48.

MS (Acc) m/z = 165.07887 (M^+); $C_9H_{11}NO_2$ requires 165.07898.

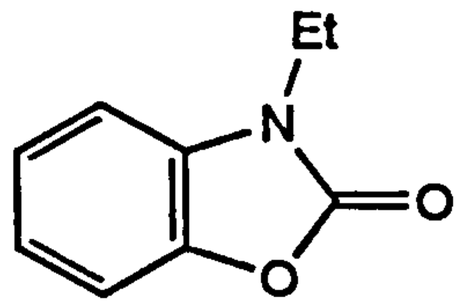
MS (EI) m/z = 165 (M^+); $C_9H_{11}NO_2$ requires 165.08.

^{1}H NMR (300MHz, $CDCl_3$): δ, 1.84-1.94 (3H, s, CH_3-CO), 3.18-3.30 (3H, s, CH_3-N), 6.88-6.95 (1H, t, Ar-**H**), 7.02-7.07 (1H, d, Ar-**H**), 7.07-7.12 (1H, d, Ar-**H**), 7.32-

7.28 (1H, t, Ar-H).

Retention time = 5.2 mins (90 % MeCN $_{(aq)}$; 0.5 mL.min^{-1}).

3-Ethylbenzoxazolinone (50)



(50)

2-Chloro-3-ethylbenzoxazolium tetrafluoroborate (0.0570 g; 0.212 mmol) was dissolved in deuterium oxide and a ^{1}H NMR spectrum taken. After extraction into dichloromethane and drying (magnesium sulfate) the solvent was removed and a mass spectrum, ^{1}H NMR and microanalysis of the orange compound were run.

Found: C, 66.00; H, 5.60; N, 8.62. $C_9H_9NO_2$ requires: C, 66.23; H, 5.56; N, 8.59.

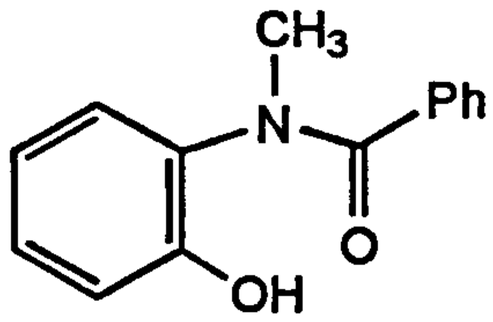
MS (EI) m/z = 163 (M^+); $C_9H_9NO_2$ requires: 163.06.

^{1}H NMR (300MHz, $CDCl_3$): δ, 1.20-1.40 (3H, t, CH_3), 3.70-3.90 (2H, q, CH_2), 6.90-7.20 (4H, m, Ar-H).

^{1}H NMR (300MHz, D_2O): δ, 1.10 (3H, t, CH_3), 3.65 (2H, q, CH_2), 6.90-7.10 (4H, m, Ar-H).

Retention time = 5.9 mins (90 % MeCN $_{(aq)}$; 0.5 mL.min^{-1}).

***N*-(2-Hydroxyphenyl)-*N*-methyl-benzamide (51)**



(51)

2-Phenyl-3-methylbenzoxazolium tetrafluoroborate (0.0826 g; 0.278 mmol) was dissolved in water (5.0 mL) and left to stand for seven days. A white precipitate was formed which was removed by filtration to give the title compound.

mp = 155-6°C; Lit.[20] = 158-159°C.

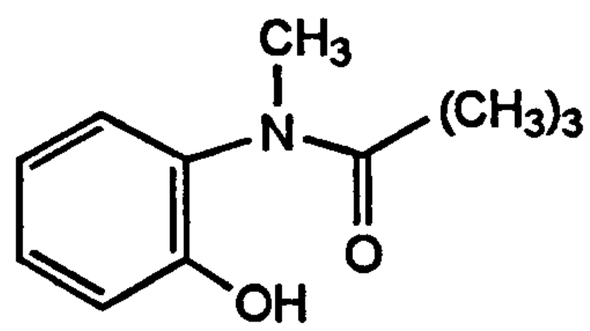
MS (EI; Acc) m/z = 227.09511 (M^+); $C_{14}H_{13}NO_2$ requires: 227.09464.

^{1}H NMR (300MHz, $CDCl_3$): δ, 3.30 (3H, s, CH_3-N), 6.69 (1H, t, Ar-H), 6.88 (1H, d,

Ar-H), 7.01 (2H, m, Ar-H), 7.19 (3H, m, Ar-H), 7.36 (2H, d, Ar-H), 8.90 (1H, s, Ar-OH).

Retention time = 5.2 mins (90 % MeCN $_{(aq)}$; 0.5 mL.min^{-1}).

_N_-(2-Hydroxyphenyl)-_N_-methyl-2', 2'-dimethylpropanamide (52)



(52)

2-*tert*-Butyl-3-methylbenzoxazolium tetrafluoroborate (0.85 g; 3.07 mmol; 1.00 eq) was dissolved in acetonitrile (10 cm^3) and stirred vigorously whilst aqueous potassium carbonate solution (2.70 g in 3.20 cm^3; 19.54 mmol; 6.36 eq) was added. After 17 hours stirring at room temperature the suspension was diluted with acetonitrile (90 cm^3), dried (magnesium sulfate) and filtered. Solvent removal yielded a yellow solid, which was washed with ether to give white crystals (0.48 g; 76 %).

mp = 168°C (decomp.)

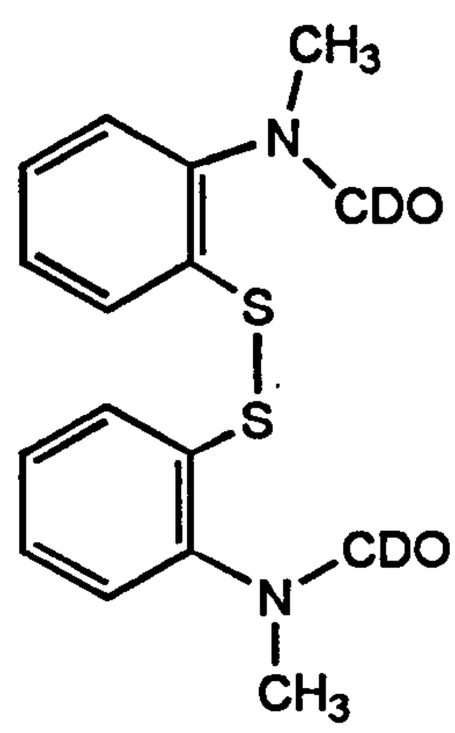
Found C, 69.38; H, 8.31, N, 6.68. $C_{12}H_{18}NO_2$ requires: C, 69.54; H, 8.27; N, 6.75.

MS (EI) m/z = 207 (M^+); $C_{12}H_{18}NO_2$ requires: 207.

^{1}H NMR (300MHz, D^6 acetone): δ, 1.00 (9H, s, C(**CH$_3$**)$_3$), 3.05 (3H, s N-**CH$_3$**), 6.90 (1H, t, Ar-H), 7.00 (1H, d, Ar-H), 7.20 (2H, m, Ar-H), 8.50 (1H, s, ArOH).

Retention time = 6.3 mins (80 % MeCN $_{(aq)}$; 0.5 mL.min^{-1})

***Bis*-(2-(*N*-formyl-*N*-methylamino)phenyl)disulfide (bideuterated) (59)[21, 22]**



(59)

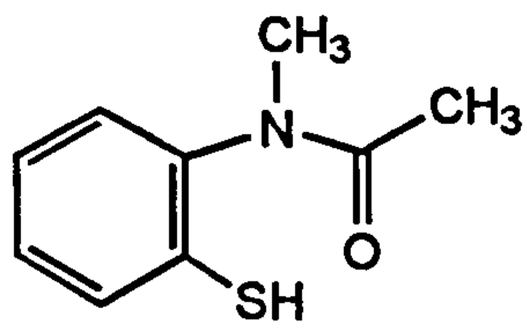
3-Methylbenzothiazolium tetrafluoroborate (0.0376 g; 0.158 mmol; 1.00 eq) was dissolved in deuterium oxide and a ^{1}H NMR spectrum was run after 2.5 hours. Then a small amount of potassium carbonate (0.0527g; 0.381 mmol; 2.40 eq) was added to the solution and a ^{1}H NMR spectrum was run after 7 days at room temperature. The solution was then extracted with DCM and the organic layer evaporated to dryness. ^{1}H NMR and mass spectra of the yellow residue were run.

MS (EI) m/z = 167 (M^+, 81.28 %), 168 (79.31), 334 (5.11). C_8H_9NOS requires 167.04; $C_{16}D_2H_{14}N_2O_2S_2$ requires 334.08.

^{1}H NMR (300MHz, $CDCl_3$): δ, 3.20 (s, 3H, NCH_3), 7.10 (1H, d, Ar-**H**), 7.30 (2H, m, Ar-**H**), 7.60 (1H,d, Ar-**H**).

Retention time = 3.6 mins (80 % MeCN $_{(aq)}$; 0.5 mL.min^{-1})

_N_-(2-Mercaptophenyl)-_N_-methyl-acetamide (60)



(60)

2,3-Dimethylbenzothiazolium tetrafluoroborate (0.0307 g; 0.122 mmol; 1.00 eq) was dissolved in distilled water (9.0 mL) and left to stand for 4 hours. TLC showed that no reaction had occurred so sodium carbonate (0.028 g; 0.264 mmol; 2.16 eq) was added to the solution. After 16 hours the mixture was extracted with DCM, dried and the solvent was removed to give a white solid.

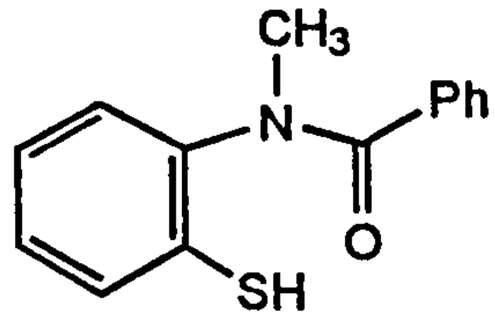
MS (EI) m/z = 181 (20.6 %), 148 (100.0 %), 138 (53.6); $C_9H_{11}NOS$ requires 181.06.

^{1}H NMR (300MHz, $CDCl_3$): δ, 1.85 (3H, s, CH_3-CO), 3.25 (3H, s, CH_3-N), 7.16-7.21 (1H, m, Ar-**H**), 7.27-7.38 (2H, m, Ar-**H**), 7.57-7.62 (1H, m, Ar-**H**).

Found: C, 59.90; H, 5.52; N, 7.67. $C_{18}H_{20}N_2O_2S_2$ requires: C, 59.97; H, 5.59; N, 7.77.

Retention time = 3.6 mins (90 % MeCN $_{(aq)}$; 0.5 mL.min^{-1})

_N_-(2-Mercapto-phenyl)-_N_-methylbenzamide (61)



(61)

2-Phenyl-3-methylbenzothiazolium tetrafluoroborate (0.1095 g; 0.350 mmol; 1.00 eq) was dissolved in CH_3CN/ H_2O (1: 2) and sodium carbonate (0.0501 g; 0.473 mmol; 1.35 eq) added. The solution was stirred overnight until the mediator was consumed, when it had become yellow in colour. Removal of acetonitrile and extraction in to DCM gave some yellow material (0.0271 g), which was washed with ethyl acetate to leave white crystals. The aqueous layer was allowed to stand for one week and a crop of white crystals was precipitated (0.0575 g; 68 %).

mp = 157-159°C.

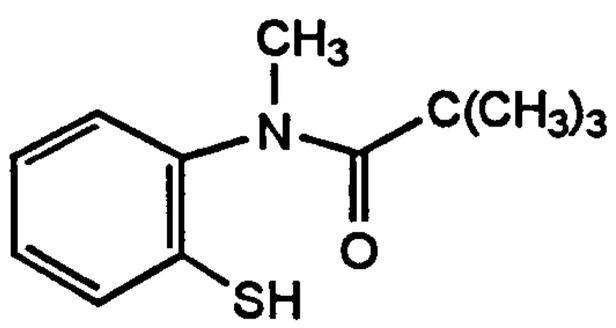
Found C, 69.27; H, 5.06, N, 5.61. $C_{28}H_{24}N_2O_2S_2$ requires: C, 69.40; H, 5.00; N, 5.78.

MS (EI; Acc) m/z = 243.07165 (M^+); $C_{14}H_{13}NOS$ requires: 243.07179.

^{1}H NMR (300MHz, $CDCl_3$): δ, 3.40 (3H, s, CH_3-N), 6.94 (1H, d, Ar-H), 7.12 (4H, s, Ar-H), 7.26 (2H, s, Ar-H), 7.37 (2H, m, Ar-H).

Retention time = 3.4 mins (90 % MeCN $_{(aq)}$; 0.5 mL.min^{-1}).

_N_-(2-Mercapto-phenyl)-_N_-methyl-2',2'-dimethylpropionamide (62)



(62)

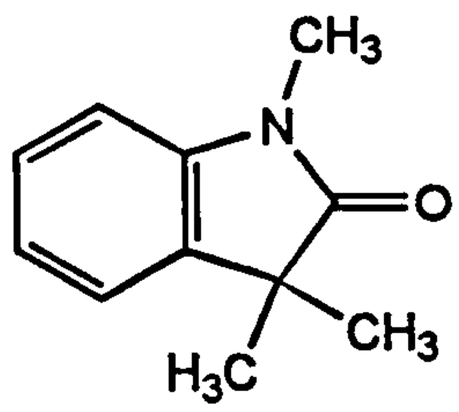
2-*tert*-Butyl-3-methylbenzothiazolium tetrafluoroborate (0.0740 g; 0.236 mmol) was dissolved in CH_3CN/ H_2O (1: 2) and sodium hydrogen carbonate (0.2007 g; 2.39 mmol; 10.1 eq) added. The mixture was allowed to stand for 7 days; after the acetonitrile was removed a white precipitate appeared. The mixture was partitioned between DCM and water, after drying and solvent removal a white solid was obtained (0.0285 g; 54 %).

MS (EI; Acc) m/z = 223.10256 (M^+); $C_{12}H_{17}NOS$ requires: 223.10309.

^{1}H NMR (300MHz, $CDCl_3$): δ, 1.13 (9H, s, $C(CH_3)_3$), 3.24 (3H, s N-CH_3), 7.19 (1H, t, Ar-H), 7.23-7.36 (2H, m, Ar-H), 7.53 (1H, s (br), Ar-H).

Retention time = 6.5 mins (90 % MeCN $_{(aq)}$; 0.5 mL.min^{-1}).

1,3,3 Trimethyloxindole (64)[23]



(64)

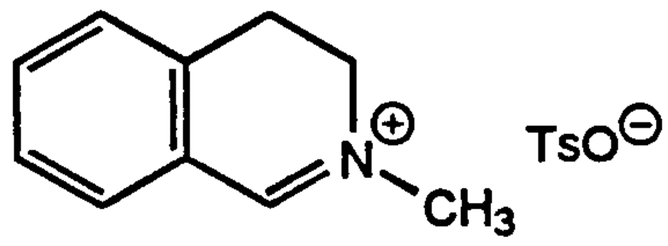
1,2,3,3-Tetramethylindoleninium tosylate (0.0437 g; 0.0126 mmol) was dissolved in deuterium oxide (4.0 mL) and a ^{1}H NMR spectrum run after 7 days at room temperature, which revealed the exchange of the 2-methyl protons (peak at 2.90 disappeared) for deuterons. The addition of a small amount of potassium carbonate led to the formation of a complex mixture. Extraction into DCM, drying (magnesium sulfate) and removal of solvent yielded crude 1,3,3 trimethyloxindole.

MS (EI) m/z =175 (M^+) + high molecular weight material >1000. $C_{11}H_{13}NO$ requires 175

^{1}H NMR (300MHz, $CDCl_3$): δ, 1.37 (6H; s; CH_3), 3.22 (3H; s; NCH_3) 6.85 (1H, d, Ar-H), 7.06 (1H, t, Ar-H), 7.21 (1H, d, Ar-H), 7.27 (1H, t, Ar-H).

Retention time = 6.9 mins (90 % MeCN $_{(aq)}$; 0.5 mL.min^{-1}); 7.5 mins (80 % MeCN $_{(aq)}$; 0.5 mL.min^{-1}).

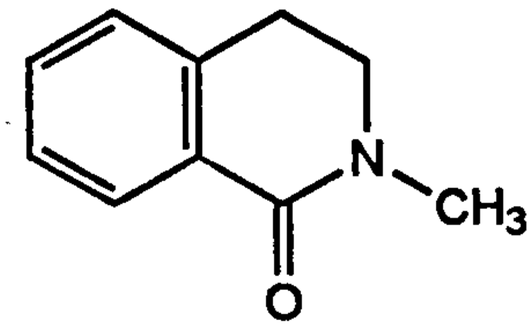
***N*-Methyl-3, 4-dihydroisoquinolinium tetrafluoroborate & tosylate (54)**



(54)

These compounds were supplied by Unilever Research Limited, Port Sunlight.

2-Methyl-3,4-dihydro-2*H*-isoquinolin-1-one (55)

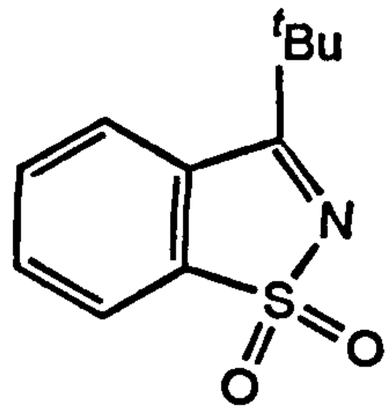


(55)

This compound was supplied by Unilever Research Limited, Port Sunlight.

Retention time = 6.5 mins (80 % $MeCN_{(aq)}$; 0.5 $mL.min^{-1}$)

3-*t*-Butyl-1, 2-benzisothiazole-1,1-dioxide (65)

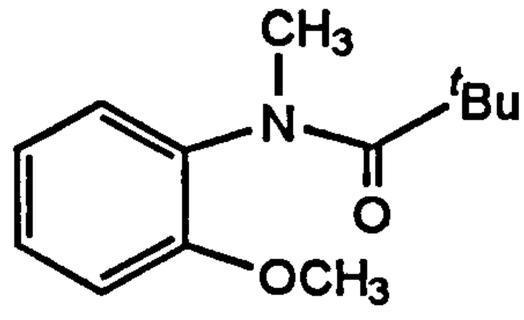


(65)

This compound was supplied by Dr. H. Vahedi, The University Of Liverpool.

Retention time = 7.2 mins (80 % $MeCN_{(aq)}$; 0.5 $mL.min^{-1}$)

***N*-(2- Methoxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide (53)**



(53)

N-(2-Hydroxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide (0.50 g; 2.41 mmol; 1.00 eq) was mixed with potassium carbonate (0.67 g; 4.85 mmol; 2.01 eq). Acetone (6 cm^3) was added, followed by methyl iodide (0.6 cm^3; 1.36 g; 9.58 mmol; 3.9 eq) and the mixture was refluxed for 19 hours. After solvent removal dichloromethane was added and the suspension filtered. Removal of DCM gave a yellow solid (0.51 g; 96 %; crude).

mp = 71-3°C.

Found: C, 70.43; H, 8.66; N, 6.31. $C_{13}H_{19}NO_2$ requires: C, 70.56; H, 8.65; N, 6.33.

MS (EI) m/z = 221 (M^+); $C_{13}H_{19}NO_2$ requires 221.

^{1}H NMR (300MHz, $CDCl_3$): δ, 1.01 (9H, s, $CO(CH_3)_3$), 3.13 (3H, s, CH_3-N), 3.83 (3H, s, CH_3-O), 6.89-6.98 (2H, t, Ar-H), 7.16-7.21 (1H, d, Ar-H), 7.28-7.35 (1H, t, Ar-H).

IR: ν_{max}: 2935 (s), 1651, (m), 1595 (w), 1502 (m), 1463 (s), 1378 (m), 1293 (w), 1244 (w), 1215(w), 1103 (w), 751 (w).

Retention time = 8.6 mins (90 % MeCN $_{(aq)}$; 0.5 mL.min^{-1})

Treatment of *N*-(2-hydroxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide (52) with sodium percarbonate

N-(2-Hydroxyphenyl)-*N*-methyl-2', 2'-dimethylpropanamide (0.0837 g; 0.409 mmol; 1.00 eq) was dissolved in d^4 methanol (6.0 mL). This solution was added to sodium percarbonate (0.2223 g; 1.42 mmol; 3.50 eq) and stirred vigorously. After 1 hour a yellow colour had developed, but no change could be observed by TLC. The solution was stirred for a further 17 hours and a ^{1}H NMR spectrum was run. Although the solution had become a deep red colour, the ^{1}H NMR spectrum showed no change.

7.7 Derivation of equations

For **Scheme 5.3**:

a)

$$k_{-3} \text{ slow; } k_{-1} \text{ slow}$$
$$-\delta[S]/\delta t = k_2 [A] [S]$$
$$\delta[A]/\delta t = k_1 [M] [P] - k_{-1} [A] - k_2 [A] [S] = 0$$
$$-\delta[S]/\delta t = \{k_2 [S] k_1 [M] [P]\} / \{ k_{-1} + k_2 [S]\}$$
$$\approx k_1 [M] [P]$$
$$[M] = [M]_0 \exp (-k_3 t)$$
$$-\delta[S]/\delta t = k_1 [P] [M]_0 \exp (-k_3 t)$$
$$[P] = \text{constant}$$
$$\Rightarrow [S] = \{k_1' [M]_0 / k_3\} \exp (-k_3 t) + C$$
$$t = \infty$$
$$[S]_\infty = C$$
$$\Rightarrow [S] - [S]_\infty = \{k_1' [M]_0 / k_3\} \exp (-k_3 t)$$
$$\Rightarrow \textit{ln} \{[S] - [S]_\infty\} = (-k_3 t) + \{k_1' [M]_0 / k_3\} \quad \textbf{[14]}$$

b)

$$-\delta[S]/\delta t = k_2 [A] [S]$$
$$\approx k_1 [M] [P]$$
$$[A] \approx [I] \approx 0$$
$$\Rightarrow [M]_0 = [M] + [D]$$
$$= [M] \{1 + ([D]/ [M])\}$$
$$= [M] \{1 + (1/ K)\}$$
$$\Rightarrow [M] = [M]_0 / \{1 + (1 / K)\}$$
$$\Rightarrow -\delta[S]/\delta t = \{k_1 [P] [M]_0 \} / \{1 + (1 / K)\} \quad \textbf{[15]}$$
$$= \text{constant}$$

From **Scheme 5.4**:

a)

$$-\delta[S]/\delta t = k_2 [A] [S]$$
$$\approx k_1 [M] [P]$$
$$= k'$$
$$[S] = [S]_0 - k't \quad \textbf{[16]}$$

b)

$$-\delta[S]/\delta t = k_2 [A] [S]$$
$$\approx k_1 [M] [P]$$
$$\text{If } k_3 \text{ is small} \Rightarrow [M]_0 = [M] + [D]$$
$$\Rightarrow -\delta[S]/\delta t = k_1 \{[M]_0 - [D]\}$$
$$\approx k_1 \{[M]_0 - [SO]\}$$

$$= k_1 \{[M]_0 - \Delta[S]\}$$
$$\Rightarrow - ln \{[M]_0 - \Delta[S]\} = k_1 t + c$$
$$\Rightarrow c = - ln \{[M]_0$$
$$\Rightarrow ln \{[M]_0/ ([M]_0 - \Delta[S])\} = - k_1 t \quad \textbf{[17]}$$

For competitive oxidations (**chapter 5**):

$$\delta[P_X]/\delta t = k_X [A] [S_X] = - \delta[S_X]/\delta t$$
$$\delta[P_H]/\delta t = k_H [A] [S_H] = - \delta[S_H]/\delta t$$
$$\Rightarrow \delta[S_X]/\delta[S_H] = k_X[S_X]/ k_H[S_H]$$
$$\Rightarrow \delta[S_X]/[S_X] = k_X \delta[S_H]/ k_H [S_H]$$
$$\therefore ln [S_X] = (k_X ln [S_H]/ k_H) + C$$
$$\text{If } [S_X] = [S_X]_0 \text{ and } [S_H] = [S_H]_0$$
$$\Rightarrow ln [S_X]_0 = (k_X ln [S_H]_0/ k_H) + C$$
$$\therefore ln ([S_X]/ [S_X]_0) = (k_X/ k_H) (ln ([S_H]/ [S_H]_0)$$
$$\Rightarrow k_X/k_H = ln ([S_X]/[S_X]_0)/ ln ([S_H]/[S_H]_0)$$
$$= ln ([S_X]_0-[P_X]/[S_X]_0)/ ln ([S_H]_0-[P_H]/[S_H]_0)$$
$$= ln (1-[P_X]/[S_X]_0)/ ln (1-[P_H]/[S_H]_0) \quad \textbf{[20]}$$

7.8 Propagation Of Error (example)

Weight of sulfoxide = 0.1011 ± 0.0001 g

Volume of solvent = 0.1000 ± 0.0001 L

% error (sulfoxide) = 100 x (0.0001/0.1011)
= 0.099 %

% error (solvent) = 100 x (0.0001/0.1000)
= 0.100 %

% error (total) = $(0.099^2 + 0.100^2)^{1/2}$
= 0.141 %

Conc. (sulfoxide) = 1.011 ± 0.141 %
1.011 ± 0.001 $g.L^{-1}$ *(stock solution)*

After dilution:

% error (solvent) = 100 x (0.0001/0.1000)
= 0.100 %

% error (total) = $(0.141^2 + 0.100^2)^{1/2}$
= 0.173 %

Conc. (sulfoxide) = 0.0778 ± 0.173 %
0.0778 ± 0.0001 $g.L^{-1}$

Conc. (biphenyl) = 0.0346 ± 0.263 %
0.0346 ± 0.0001 $g.L^{-1}$

Conc. (sulfoxide)/ Conc. (biphenyl) = 0.0778 / 0.0346
= 2.249

% error = $(0.173^2 + 0.263^2)^{1/2}$
= 0.315 %

Conc. (sulfoxide)/ Conc. (biphenyl) = 2.2486 ± 0.0071

Error (UV detector) = 1×10^{-5} Au
% error (UV detector) = $100 \times (1 \times 10^{-5} / 0.5000)$
= 0.002 %
% error (gradient) = $(0.315^2 + 0.002^2)^{1/2}$
= 0.315 %

error (time) ≈ 1 sec
% error (time) = 100 x (1/ 3600)
= 0.028 %
% error (rate) = $(0.315^2 + 0.028^2)^{1/2}$
= 0.316 %

Effect of trendline order upon the calculated rate

In order to confirm how the type of polynomial used for linear regression analysis influences the observed rate of reaction, a particular set of data was examined and fit to different orders of polynomial. The observed rates are shown in **Table 7.1**.

Table 7.1 Table to show how the observed rate is influenced by the choice of polynomial

Order Of Polynomial	Observed Rate (t=0)	R^2
Linear	1.2×10^{-5} mol.$L^{-1}S^{-1}$	0.990
2nd	1.0×10^{-5} mol.$L^{-1}S^{-1}$	0.992
3rd	1.6×10^{-5} mol.$L^{-1}S^{-1}$	0.996
4th	1.9×10^{-5} mol.$L^{-1}S^{-1}$	0.996

Data from entry 2, **Table 5.5**

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