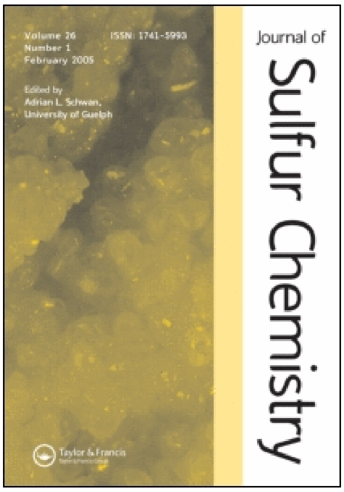


Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Synthesis of Aryl Sulfones

Robert S. Ward[a]; Richard L. Diaper[a]
[a] Chemistry Department, University of Wales Swansea, Swansea, UK

To cite this Article Ward, Robert S. and Diaper, Richard L.(2001) 'Synthesis of Aryl Sulfones', Journal of Sulfur Chemistry, 22: 3, 251 — 275
To link to this Article: DOI: 10.1080/01961770108047963
URL: http://dx.doi.org/10.1080/01961770108047963

Sulfur Reports, 2001, Vol. 22, pp. 251–275
Reprints available directly from the publisher
Photocopying permitted by license only

Published by license under
the Harwood Academic Publishers imprint,
part of Gordon and Breach Publishing,
a member of the Taylor & Francis Group.

SYNTHESIS OF ARYL SULFONES

ROBERT S. WARD* and RICHARD L. DIAPER

Chemistry Department, University of Wales Swansea,
Singleton Park, Swansea SA2 8PP, UK

(Received 12 January 2000; In final form 15 February 2000)

Methods available for the synthesis of diaryl and monoaryl monoalkyl sulfones are reviewed. The main methods employed involve alkylation of salts of sulfinic acids, acid-catalysed condensation of sulfonic acids with aromatic hydrocarbons, and oxidation of diaryl and alkyl aryl sulfides. Oxidation by peracids, *N*-oxides (catalysed by tetra-*n*-propylammonium perruthenate), periodate (catalysed by ruthenium trichloride), and oxone® (potassium hydrogen persulfate), are highlighted.

Keywords: Sulfinic acids; Alkylation; Sulfonic acids; Sulfides; Oxidation; Oxone®; Potassium hydrogen persulfate

CONTENTS

---

*Corresponding author.

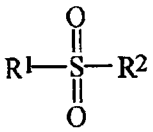
1. DIRECT SYNTHETIC ROUTES TO SULFONES

This review is concerned with the strategies used in the preparation of symmetrical diaryl, and unsymmetrical diaryl and aryl alkyl, sulfones. Direct synthetic routes to sulfones are discussed, together with the various methods available for the selective oxidation of the corresponding sulfides to sulfones.

Sulfones have the general formula **1** in which the carbon substituents can be any combination of alkyl, aryl, alkenyl, or alkynyl groups. Generally the sulfone group is both chemically and thermally stable, being resistant to oxidation, and only reduced to the corresponding sulfide with great difficulty [1].

1.1. Alkylation of Sulfinic Acids

Sulfinic acids probably exist as the hydroxy tautomer **2** as opposed to **3** and any equilibrium is expected to lie well to the left (Eq. (1)). Free sulfinic acids are unstable and can disproportionate to a thiol sulfonate and a sulfonic acid. Therefore they are often used as the more stable sodium salts [2].



$$R^1{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}{-}R^2$$

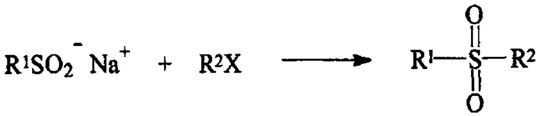
1

R^1 and/or R^2 = alkyl or aryl

$$R\overset{\overset{\displaystyle O}{\|}}{S}OH \rightleftharpoons R\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}H \qquad (1)$$

2 **3**

The alkylation of sulfinic acid salts (Eq. (2)) has been used to prepare aryl alkyl sulfones using a variety of alkylating agents [1,3,4]. Improved yields have however been reported in the alkylation of *p*-toluenesulfinate anion when the acid was used as the tetra-*n*-butylammonium salt (Tab. I) [3] as opposed to the sodium salt [4].

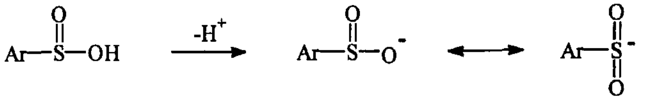


$$R^1SO_2^- \, Na^+ + R^2X \longrightarrow R^1-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-R^2 \qquad (2)$$

The tetra-*n*-butylammonium sulfinate salt is prepared by extraction of a concentrated aqueous solution of tetra-*n*-butylammonium bromide and sodium-*p*-toluenesulfinate with CH_2Cl_2 followed by removal of the solvent to give the reagent as a crystalline solid [3].

Solutions of the tetra-*n*-butylammonium sulfinate in THF were found to react smoothly with a series of primary alkyl halides at 20–40°C. The sulfone products were obtained in excellent yields in reaction times of 2–4 hours (Tab. I) [3]. In contrast, the reaction of methyl iodide with the corresponding sodium salt of *p*-toluenesulfinic acid gives a lower yield of the sulfone, even at elevated temperatures and with longer reaction times (22 h in DMF, 50%; 23 h in MeOH, 77%) [4]. A further advantage in using the tetra-*n*-butylammonium salt is reduced competition from *O*-alkylation in its reaction with chloromethyl methyl ether [3]. When the sodium salt was used the corresponding sulfone was obtained in only 15% yield [5].

When alkylation occurs on oxygen as opposed to sulfur, the products are sulfinate esters. This is due to the ambient nature of the sulfinate anion (Eq. (3)).

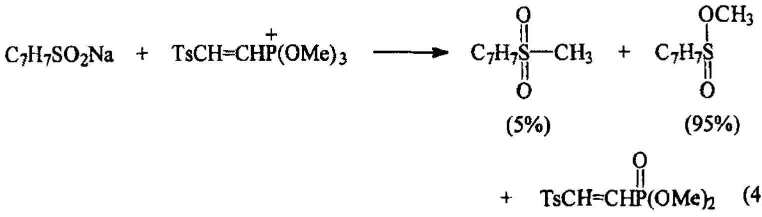


$$Ar-\overset{\overset{\displaystyle O}{\|}}{S}-OH \xrightarrow{-H^+} Ar-\overset{\overset{\displaystyle O}{\|}}{S}-O^- \longleftrightarrow Ar-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}{}^- \qquad (3)$$

TABLE I Alkylation of tetra-*n*-butylammonium *p*-toluenesulfinate in THF [3]

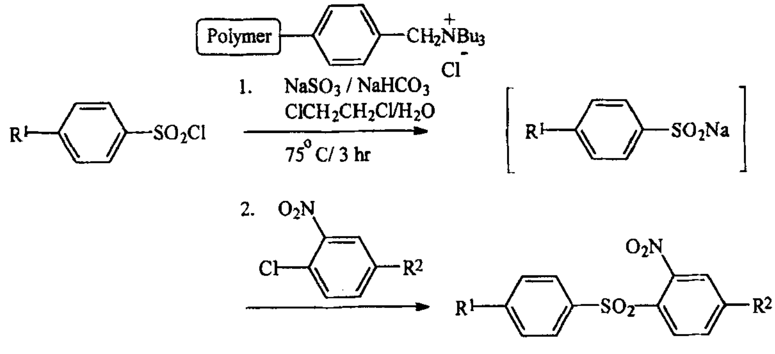
Alkylating agent	*Product*	*% yield*
MeI	$C_7H_7SO_2Me$	93
$CH_2{=}CHCH_2Br$	$C_7H_7SO_2CH_2CH{=}CH_2$	80
$PhCOCH_2Br$	$C_7H_7SO_2CH_2COPh$	81
CH_2Br_2	$C_7H_7SO_2CH_2Br$	89
CH_3OCH_2Cl	$C_7H_7SO_2CH_2OCH_3$	59

O-Alkylation tends to occur in addition to *S*-alkylation when a hard electrophile such as an alkoxyphosphonium salt is used as the alkylating agent. The result is a mixture of sulfinate ester and sulfone products (Eq. (4)) [4]. The use of softer electrophiles such as methyl iodide under similar reaction conditions leads almost exclusively to the sulfone product [4].



$$C_7H_7SO_2Na + TsCH{=}CH\overset{+}{P}(OMe)_3 \longrightarrow \underset{(5\%)}{C_7H_7S(=O)_2{-}CH_3} + \underset{(95\%)}{C_7H_7S(=O){-}OCH_3} + TsCH{=}CHP(=O)(OMe)_2 \quad (4)$$

Despite the references to alkylation of aromatic sulfinate salts with alkyl halides in the preparation of aryl alkyl sulfones, there appear to be no references to arylation of aromatic sulfinate salts with activated aromatic halides, as a route to diaryl sulfones. Unsymmetrical diaryl sulfones have however been synthesised by the reaction of activated aromatic halides and a sodium arenesulfinate salt, generated *in situ* from the reaction of an arenesulfonyl chloride with sodium sulfite and sodium bicarbonate in 1,2-dichloroethane and water, in the presence of a phase transfer catalyst (PTC) (Scheme 1) [6]. The polymer supported catalyst used for this reaction was tri-*n*-butylammonium



Scheme 1[6] ($R^1 = CH_3$, F; $R^2 = NO_2$, CHO, $COCH_3$)

SCHEME 1

chloride bound to a polystyrene matrix. The method proved to be an excellent route to unsymmetrical diaryl sulfones, using only mild conditions and achieving yields of 82–94%. The presence of electron-withdrawing groups did not significantly affect the reaction. No reaction was observed in the absence of the PTC.

The advantage of using a polymer bound catalytic system as opposed to soluble tetra-*n*-butylammonium chloride was in lowering the catalyst cost through its subsequent recovery. The catalyst was simply recovered by filtration and could be used again after washing with ethanol, water and ether.

A liquid–liquid phase transfer method for the alkylation of sodium *p*-toluenesulfinate with a range of alkyl halides had been reported prior to this method [7]. The reactants were refluxed in a mixture of benzene, acetone and water in the presence of tetra-*n*-butylammonium bromide or iodide as the PTC. The procedure was restricted to primary bromides and iodides, secondary iodides, or activated chlorides and bromides such as allylic, benzylic and α-carbonyl compounds (Tab. II) [7]. Once again no reaction was observed in the absence of the PTC.

The sulfinic acid routes to sulfones outlined above are however unsuitable for the preparation of many diaryl sulfones. This is because the reported synthesis of diaryl sulfones under PTC conditions [7] is not viable on a preparative scale and other strategies should be considered before embarking on a study of sulfinic acid arylation with activated aromatic halides.

1.2. Condensation of Sulfonic Acids with Aromatic Hydrocarbons

A route that has proven successful for the synthesis of a wide range of diaryl sulfones is the condensation of an arylsulfonic acid with an

TABLE II Alkylation of sodium *p*-toluenesulfinate in the presence of TBAB as PTC in refluxing benzene acetone water [7]

Alkyl halide	*Reaction time (h)*	*% yield of sulfone*
$CH_3(CH_2)_5Cl$	24	0
$CH_3(CH_2)_6Br$	8	85
$(CH_3)_2CHI$	6	89
CH_3COCH_2Cl	6	94
$CH_2{=}C(CH_3)CH_2Cl$	12	71

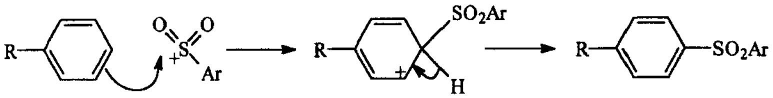
aromatic hydrocarbon in the presence of a dehydrating agent [8 – 10] (Eq. (5)). The use of a dehydrating agent has been shown to be more successful than direct condensation of these compounds at high temperatures which is reported to result in desulfonation of the molten sulfonic acid [11].

$$\mathrm{Ar^1SO_3H} + \mathrm{Ar^2H} \xrightarrow[\text{agent}]{\text{dehydrating}} \mathrm{Ar^1SO_2Ar^2} + \mathrm{H_2O} \qquad (5)$$

Polyphosphoric acid (PPA) was successfully used as the dehydrating agent in the synthesis of a range of diaryl sulfones, by stirring the substituted aromatic hydrocarbons with either benzenesulfonic acid or *p*-toluenesulfonic acid at 80°C in PPA for approx. 8 hours [8]. The order of reactivity for the substituted aromatic hydrocarbons was found to be mesitylene > xylene > toluene > benzene. Furthermore, deactivated aromatic compounds such as chlorobenzene did not react with *p*-toluenesulfonic acid under the same reaction conditions. These observations are consistent with an attack on the aromatic ring by a weakly electrophilic reagent, and the mechanism for sulfone formation probably involves the sulfonium cation $\mathrm{ArSO_2^+}$ (Scheme 2).

Field has reported the reaction of P_2O_5 with sulfonic acids under similar conditions in the synthesis of sulfonic anhydrides [12]. This has led to the assumption that the anhydride is probably an intermediate in the formation of the sulfone in the PPA condensation [8].

The PPA method for sulfone synthesis was later improved by Sipe *et al.* [9] who observed an enhancement in the yield of phenyl *p*-tolyl sulfone on addition of phosphorous pentoxide to the PPA and *p*-toluenesulfonic acid prior to mixing. Carrying out the reaction in an inert atmosphere was also advantageous. The improved yields observed using this modification are attributed to the ability of P_2O_5 to absorb water during the reaction, which could otherwise interfere with the formation of the sulfonium cation intermediate.



SCHEME 2

Due to the difficulties associated with the handling of PPA, notably that it is a very viscous liquid at temperatures below 60–80°C and therefore difficult to stir and manipulate, a novel alternative was developed by stirring a 1:10 solution (w/w) of P_2O_5 in methanesulfonic acid [13].

Organic compounds dissolve readily in this reaction medium and it was found to be a good substitute in some reactions classically associated with PPA; specifically in the intramolecular alkylation of olefinic acids or their lactones to form cyclopentenones and in the preparation of amides *via* the Beckmann rearrangement [11]. The active species in these reactions was not identified, but was postulated to be a very active mixed anhydride. Interestingly solutions of methanesulfonic acid and anhydride were less active and methanesulfonic acid alone was ineffective [13].

Subsequently the methanesulfonic acid/P_2O_5 reagent has been shown to be a good alternative to PPA in the synthesis of diaryl sulfones by the condensation of *p*-toluenesulfonic acid with a range of substituted aromatic hydrocarbons (Tab. III) [10].

Excellent yields of diaryl sulfones were obtained under mild reaction conditions and the reagent was found to be preferable to PPA because it was easier to handle and was easily removed in the subsequent work-up. The ready availability of starting materials, mild reaction conditions and high yields make this synthetic route an appealing strategy for the synthesis of diaryl sulfones, containing hydrocarbon substituents (see below).

As part of an investigation into the cleavage of diaryl sulfones with concentrated sulfuric acid [14], a range of diaryl sulfones **4** containing various hydrocarbon substituents have been synthesised *via* this method.

TABLE III Reaction of *p*-toluenesulfonic acid with arenes in $MeSO_3H/P_2O_5$ [10]

Arene	*Time (h)/ temp (°C)*	*% yield of sulfone*
Benzene	2/80	80
	24/20	10
Toluene	24/20	94
Mesitylene	24/20	93
Chlorobenzene	2/80	9

The reagent used for this reaction was a mixture of phosphorous pentoxide and methanesulfonic acid in the ratio of 1:10 w/w [10, 13]. In a typical reaction the glassware was dried (100°C) and assembled hot. The condensation reagent was prepared by adding dry P_2O_5 to freshly distilled methanesulfonic acid under an inert atmosphere, then stirring the solution mechanically for at least two hours until the P_2O_5 was seen to dissolve. The amount of P_2O_5 added was approximately the maximum amount soluble in the volume of methanesulfonic acid used [13], and on occasions the reagent was used with undissolved P_2O_5 remaining in the solution. This did not appear to affect the reaction in any way. The reagent was normally used soon after preparation, although it could be stored under an inert atmosphere for up to a week with no apparent decrease in its efficacy [13]. (The nitrogen atmosphere was maintained throughout the preparation of the reagent and also during the condensation reaction).

The aromatic hydrocarbon was then added to the reagent, which also acted as an effective solvent, and stirring continued. When heating was required, the flask was fitted with a reflux condenser and the nitrogen atmosphere was maintained. The reaction was monitored by tlc of removed aliquots, after a mini work-up. The reaction mixture was then poured into excess ice-water and most of the sulfone products were isolated by filtration as crystalline or amorphous solids. The condensation reagent was soluble in water and thereby removed during the work-up. Recrystallisation from hot EtOH afforded the products, which were identified by standard analytical techniques. The synthesis was found to be suitable for the preparation of 4,4′-dimethyldiphenyl sulfone and a range of unsymmetrical diaryl sulfones up to a multigram scale (Tab. IV) [14].

Reasonable yields of sulfone were obtained when *t*-butylbenzene, phenylcyclohexane and 1-phenyldodecane were used as the hydrocarbons in the reaction with *p*-toluenesulfonic acid. However the reaction of chlorobenzene with 4-chlorobenzenesulfonic acid, and bromobenzene with 4-bromobenzenesulfonic acid, gave poor yields of sulfone (Tab. IV). These observations are in agreement with those previously reported in the literature [10]. The reaction is largely unaffected by steric hindrance, but deactivated benzene rings such as chlorobenzene and bromobenzene are resistant towards condensation. This is probably due to the electron deficient aromatic ring of these

TABLE IV Sulfone synthesis by condensation of an aromatic sulfonic acid with a monosubstituted benzene derivative in $MeSO_3H/P_2O_5$ [14]

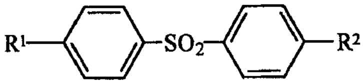
Sulfonic acid	*Aromatic compound*	*Reaction conditions*	*% yield of sulfone*	*M.P. (°C)*
p-$MeC_6H_4SO_3H$	$PhCH_3$	24 h/ambient	64	148–156
	PhC_6H_{11}	24 h/ambient	28	119–120
		3 h/80°C	58	
	$PhBu^t$	7 days/ambient	98	
		24 h/80°C	86	
	$PhC_{12}H_{25}$	6 h/80°C	3	64–65
		24 h/80°C	51	
p-$ClC_6H_4SO_3H$	PhCl	24 h/80°C	7	140–150
p-$BrC_6H_4SO_3H$	PhBr	16 h/80°C	3	170–172
		24 h/80°C	15	

compounds being less susceptible to attack by the weakly electrophilic sulfonium cation.

This method has proven excellent for the synthesis of some unsymmetrical diaryl sulfones and importantly it can be carried out on a preparative scale. The method is simple, the cost of the starting materials is low, and reasonable sulfone yields are obtained under mild reaction conditions. Heating the reaction mixture is effective in shortening the reaction time, and often leads to an increased product yield. The range of symmetrical diaryl sulfones accessible *via* this route is however constrained by the availability of the sulfonic acid starting materials. However the ready availability of various aromatic hydrocarbons has meant that a number of unsymmetrical diaryl sulfones can be prepared (Tab. IV) [14].

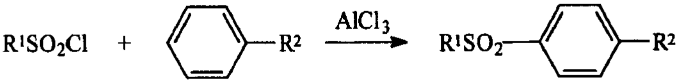
1.3. Friedel Crafts Sulfonylation and Related Reactions

One method frequently employed for the preparation of aryl sulfones is Friedel–Crafts type sulfonylation, in which an arene and a sulfonyl halide react in the presence of a Lewis acid catalyst [15]. For example, methanesulfonyl chloride has been used with equivalent amounts of $AlCl_3$, $FeCl_3$ or $SbCl_5$ to form methyl sulfones. $AlCl_3$ was found to be the superior catalyst when the reaction was carried out in an excess of the arene, which also acts as the solvent [16]. A variety of diaryl sulfones have also been synthesised from substituted arylsulfonyl halides and nucleophilic aromatic compounds (Eq. (6)) [16–19]. The presence of electron withdrawing substituents such as NO_2, F, Cl and Br in the *para* position of the benzene ring, increases the *ortho* content of the product mixture from around 28% up to 51% in reactions with toluene. In contrast electron donating groups such as CH_3 and OCH_3 produce an isomer distribution containing in excess of 80% of the *para* substituted tolyl sulfone [17]. The sulfonylation reaction has been shown to involve the formation of a 1:1 complex between the arenesulfonyl chloride and $AlCl_3$, followed by ionisation to form the sulfonium cation. The arene is subsequently attacked to produce the sulfone, which complexes with the catalyst [15-17].



4

(R^1 = alkyl, R^2 = methyl)



(6)

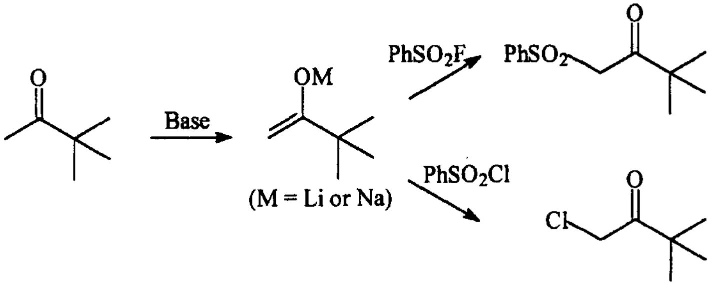
(R^1 = alkyl or aryl; R^2 = H, alkyl, Cl, Br, F, OMe)

Most recently an Fe(III) exchanged montmorillonite clay has been used as the Friedel-Crafts catalyst in the synthesis of several diaryl sulfones [20]. The reactions gave good yields (78-92%) with much increased *para* selectivity compared to reactions using $AlCl_3$. The reaction was also advantageous because it did not generate any of the solid waste associated with $AlCl_3$ and was therefore a cleaner and more environmentally friendly process. In addition the catalyst was easily recovered and could be re-used with little effect on its efficacy.

A variation on this approach involves the reaction of an organometallic reagent (*e.g.*, Grignard, organolithium, or organocopper reagent) with a sulfonyl halide or sulfonate ester (Eq. (7)) [21-24]. The sulfonyl fluoride or the phenyl ester are the substrates of choice for this transformation since competing reactions involving nucleophilic attack on the halogen or on the ester moiety are precluded.

$$R^1SO_2X \quad + \quad R^2M \quad \longrightarrow \quad R^1{-}SO_2{-}R^2 \qquad (7)$$

(R^1 and R^2 = alkyl or aryl; X = F or OPh; M = Mg, Li or Cu)



SCHEME 3

Alkyl aryl sulfones can also be prepared by reacting lithium or sodium (but not potassium) enolates with arenesulfonyl fluorides (Scheme 3) [25], and by palladium catalysed coupling of alkenyl, allyl, or *p*-methoxybenzyl tributylstannanes with arenesulfonyl chlorides (Eq. (8)) [26].

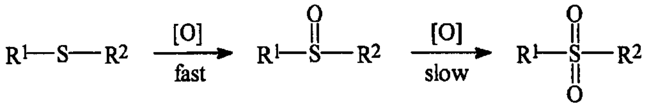
$$\mathrm{ArSO_2Cl} \quad + \quad \mathrm{Bu_3SnR} \quad \xrightarrow[\mathrm{THF}]{\mathrm{Pd(PPh_3)_4}} \quad \mathrm{ArSO_2R} \quad + \quad \mathrm{Bu_3SnCl} \qquad (8)$$

($R = PhCH{=}CH, EtO_2CCH{=}CH, CH_3CH{=}CHCH_2, p\text{-}MeOC_6H_4CH_2$, etc.)

2. OXIDATION OF SULFIDES

The condensation route and the Friedel Crafts reaction have proven useful in the synthesis of some diaryl sulfones containing hydrocarbon substituents. However the suitability of this methodology is restricted by the availability of suitable sulfonic acid starting materials. Furthermore, the method is unsuitable for the synthesis of diaryl sulfones containing electron withdrawing groups [10]. An alternative more general route to synthesise di-*p*-substituted diaryl sulfones is by oxidation of the corresponding diaryl sulfides.

The sulfur heteroatom of sulfides is susceptible to attack from electrophilic sources of oxygen. Sulfur accepts electrons into its vacant *d*-orbitals forming hypervalent sulfur compounds. The initial product of sulfide oxidation is a sulfoxide **5**, which can be further oxidised to a sulfone **6**, the second oxidation step usually requiring stronger reaction conditions (Eq. (9)).



$$R^1{-}S{-}R^2 \xrightarrow[\text{fast}]{[O]} R^1{-}\overset{\overset{O}{\|}}{S}{-}R^2 \xrightarrow[\text{slow}]{[O]} R^1{-}\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}{-}R^2 \qquad (9)$$

5 **6**

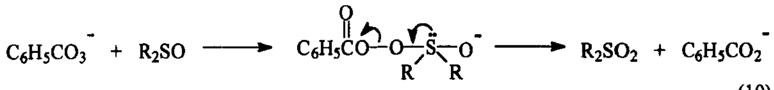
The initial oxidation is the faster of the two steps. Consequently reagents available for oxidations to sulfoxides are more varied, and the reaction conditions required are often less vigorous than those for sulfone formation.

2.1. Reagents for the Chemoselective Oxidation of Sulfides to Sulfones

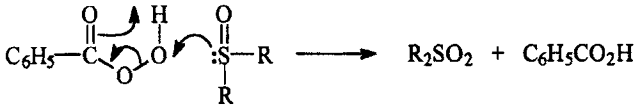
The most commonly used laboratory reagent for the oxidation of sulfides to sulfones are H_2O_2, usually in acetic acid [27] and $KMnO_4$ [15]. The hydrogen peroxide/acetic acid system has been used in the oxidation of 2-methyl-4-nitro-4′-acetamidodiphenyl sulfide to the corresponding sulfone in 80% yield [28]. A general procedure involves slow addition of an excess of H_2O_2 to a cooled solution of the sulfide, then allowing the sulfoxide to form over several hours at room temperature before heating at 100°C for a further period to yield the sulfone.

Hydrogen peroxide has also been used in conjunction with aqueous solutions of transition metal catalysts in non-acidic media to prepare 2-sulfonylethanols from their sulfides [29]. The use of tungsten, vanadium and molybdenum catalysts overcomes the problems of secondary oxidation of the sensitive hydroxy groups. The catalysts are formed *in situ* on addition of hydrogen peroxide (31%) to stirred aqueous solutions of various transition metal salts (*e.g.*, Na_2VO_4). The actual oxidising species is believed to be a peroxy form of tungstic, vanadic or molybdic acid. These react with the sulfide and sulfoxide more quickly than H_2O_2 alone, and the catalysts are subsequently regenerated *in situ* by the hydrogen peroxide [29].

Peracids such as *m*-CPBA (*m*-chloroperoxybenzoic acid) have also found extensive use in the oxidation of sulfides to sulfones. The reaction may proceed by either of two mechanisms, which is determined by the pH of the solution and is largely independent of the solvent (Eqs. (10) and (11)). The formation of the sulfone proceeds through a sulfoxide intermediate [15].



$$C_6H_5CO_3^- + R_2SO \longrightarrow C_6H_5C(=O){-}O{-}O{-}S(R)_2{-}O^- \longrightarrow R_2SO_2 + C_6H_5CO_2^- \qquad (10)$$



$$C_6H_5{-}C(=O){-}O{-}O{-}H \; + \; {:}S(=O)R_2 \longrightarrow R_2SO_2 + C_6H_5CO_2H \qquad (11)$$

Another common laboratory reagent used in the oxidation of sulfides is potassium permanganate [20, 28, 30, 31]. In the oxidation of a series of oxathiolanes [30] the reaction was carried out in a CH_2Cl_2/H_2O biphasic system with a five-fold excess of $KMnO_4$. The reaction is largely heterogeneous with the actual oxidation occurring at the phase boundary. This was implicated from the observation that there was an insignificant increase in the yield of the reaction on addition of a PTC, such as benzyltriethylammonium chloride.

PTC oxidation with aqueous $KMnO_4$, in the presence of benzoic acid has been shown to be an effective system for the oxidation of a range of sulfides to sulfones [31]. The oxidations required 1 equivalent of benzoic acid and 1 – 2 equivalents of $KMnO_4$ in addition to benzyltriethylammonium chloride (0.1 equiv.) as a PTC, and were carried out in CH_2Cl_2/H_2O at room temperature (Tab. V).

The nature of the oxidising species is not known, but was shown to be different to the species present in the absence of added benzoic acid by the oxidation of some chiral thiazolines **7**. The addition of benzoic

TABLE V Phase transfer catalysed oxidation of sulfides (R^1SR^2) with $KMnO_4$ and added benzoic acid [29]

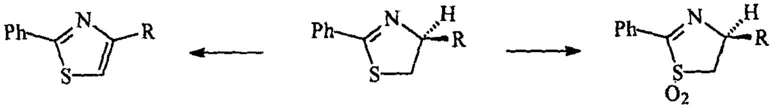
R^1	R^2	*% yield of sulfone*
Ph	$PhCH_2$	82
Et	$PhCH_2$	66
$4\text{-}ClC_6H_4$	$PhCH_2$	63
$4\text{-}O_2NC_6H_4$	Ph	71
CH_2CO_2Me	Ph	66
H	$PhCH_2$	75

acid under PTC resulted in *S*-oxidation to give *S*,*S*-dioxides **8** but gave the corresponding thiazoles **9** under the same PTC conditions in the absence of the acid (Scheme 4). The possibility of peroxybenzoic acid being formed *in situ*, as the active oxidising agent, was shown to be an unlikely explanation as treatment of (7) with $PhCO_3H$ in $CHCl_3$ gave some **8** and **9** as well as its hydrolysis products [29].

In addition to the more common laboratory reagents used to oxidise sulfides to sulfones, a number of other more novel oxidants and catalytic oxidation systems have been developed.

Any undergraduate textbook makes reference to the use of osmium tetroxide for organic oxidations, particularly in the hydroxylation of olefins. Organic chemists are also familiar with the extreme toxicity and associated handling problems of OsO_4. It was partly due to these problems that Djerassi and Engle investigated the oxidation reactions of the corresponding ruthenium compound, which was said to be less toxic to the eyes [32]. They found that RuO_4 was a more potent oxidising agent than OsO_4, reacting violently with even common solvents such as benzene, ether and pyridine. Chloroform and carbon tetrachloride were found to be the only solvents suitable for investigating the oxidising potential of this compound. Despite its reactivity, RuO_4 was found to be stable in solutions of the latter solvent for up to one year.

Ruthenium tetrachloride was shown to oxidise diphenyl sulfide at 0°C affording the sulfone and some of the corresponding sulfoxide. The sulfoxide was shown to be the intermediate in the reaction by the quantitative oxidation of diphenyl sulfoxide under the same conditions. In addition to this diaryl sulfide, the oxidation was successful with methyl *p*-tolyl sulfide and methyl benzyl sulfide where 31% and 51% of the corresponding sulfones were isolated respectively. No



9 7 8

Scheme 4
R = Pr^i, CH_2Ph, Et

SCHEME 4

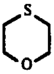
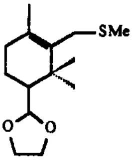
reaction was observed when osmium tetroxide was used under the same conditions [32].

Although osmium tetroxide was shown to be unreactive towards sulfides [32], it was found to have catalytic activity when used in conjunction with a tertiary amine *N*-oxide [33]. A series of sulfides were selectively oxidised to their sulfones, under mild conditions, with *N*-methylmorpholine-*N*-oxide (NMO) **10** or trimethylamine-*N*-oxide **11** in the presence of approx. 5 mol% of OsO_4 as catalyst [33]. With a 3 molar excess of amine *N*-oxide, the sulfone was formed as the only product, with no discernible amount of the sulfoxide. No oxidation occurred when either of the reagents was used separately. This indicated that the tertiary amine *N*-oxide was active in the formation or oxidative breakdown of the intermediate OsO_4/sulfur complex.

Another ruthenium salt, namely tetra-*n*-propylammonium perruthenate, *n*-Pr_4NRuO_4 (TPAP) has also been shown to be a very efficient and chemoselective catalyst for the oxidation of sulfides to sulfones in the presence of NMO as a co-oxidant (Tab. VI) [34]. The reagent was shown to be tolerant of a number of functionalities including olefinic double bonds, and gave high yields of the sulfones as the only products. For these reasons TPAP was shown to be a superior oxidant to *m*-CPBA (which caused further oxidation of the double bonds to form epoxides) for these substrates.

The reactions were carried out in acetonitrile at 40°C with 5 mole% of TPAP. Less polar solvents such as CH_2Cl_2 and THF slowed the rate

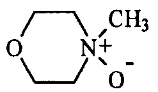
TABLE VI Oxidation of sulfides with TPAP and NMO co-oxidant (40°C) [34]

Sulfide	*Reaction time (h)*	*% yield of sulfone*
PhSMe	3	97
PhSPh	23	61
	3.5	83
	17.5	99
	3	80

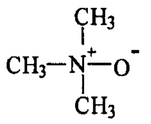
of the reaction and often led to incomplete conversion. Most of the reactions were carried out on a 1 mmol scale but one example of a large scale reaction was given.

In addition to the ruthenium compounds already mentioned [32, 34], ruthenium trichloride has been shown to be a catalyst in a number of oxidations with sodium periodate [35], and the sodium periodate-ruthenium trichloride system has been shown to be very useful for the selective oxidation of unreactive sulfides, containing the highly electron-withdrawing trifluoromethyl group [36]. The sulfones were obtained in excellent yields under ambient conditions in remarkably short reaction times (Tab. VII), with no detection of any sulfoxide. The power of this oxidation system for sulfides is highlighted by the oxidation of diphenyl sulfide which was actually complete in 20 mins. This compares very favourably with the (OsO_4–NMO) [33] or (*n*-Pr_4NRuO_4–NMO) [34] systems that required in excess of 24 hours for the same reaction.

Electron-withdrawing groups slowed the rate of the reaction, but it was unaffected by steric hindrance, as is exemplified by di-*t*-butyl sulfide which is oxidised to the sulfone in excellent yield in less than 1 hour. The reaction was exothermic and the catalytic turnover was high, requiring only approx. 0.05 mole% of $RuCl_3$ for efficient oxidation. Aqueous solutions of sodium periodate in the absence of any catalyst had previously been shown to oxidise sulfides to sulfoxides selectively (Eq. (12)) [37, 38].

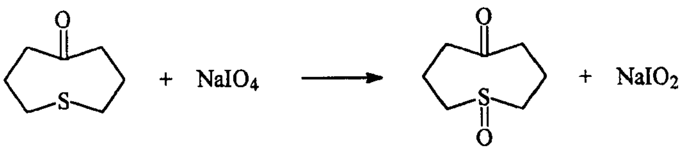


10



$$CH_3{-}\overset{CH_3}{\underset{CH_3}{\overset{+}{N}}}{-}O^-$$

11



(12)

The reaction gave excellent yields (65–99%) of sulfoxides with no observed over-oxidation to the sulfones.

TABLE VII $RuCl_3$ catalysed periodate oxidation of sulfides (R^1SR^2) [36]

R^1	R^2	*Reaction time (h)*	*% yield of sulfone*
CF_3	Ph	1	91
CF_3	*p*-$NC-C_6H_4$	12	98
Ph	Ph	1	100
p-$O_2NC_6H_4$	*p*-$O_2NC_6H_4$	1	85
t-Bu	*t*-Bu	1	84

A novel oxidant that is effective in the selective oxidation of sulfides, and is useful in the synthesis of ^{18}O-labelled sulfones is the $HOF \cdot CH_3CN$ complex [39]. The reaction is essentially one of oxygen transfer from water, *via* $HOF \cdot CH_3CN$, which is generated by bubbling fluorine through aqueous acetonitrile. Aryl alkyl and aryl benzyl sulfides are successfully oxidised to sulfones in a matter of minutes at 0°C with an excess of this oxidant (Eq. (13)). The presence of deactivating groups, such as — NO_2 in the benzene ring has little effect on the rate of the reaction.

$$R^1—S—R^2 \xrightarrow[\text{[HOF.CH}_3\text{CN]}]{F_2 + H_2O + CH_3CN} R^1—SO_2—R^2$$

$$\begin{aligned} &R = 4\text{-}CH_3C_6H_4,\ R' = Me \\ &R = 4\text{-}O_2NC_6H_4,\ R' = Me \\ &R = R' = PhCH_2,\ C_5H_9,\ Bu^t \end{aligned} \qquad (13)$$

This method of oxidation is advantageous, in that it avoids the use of oxidants containing heavy metals, and it facilitates an easy and economical route to ^{18}O-labelled sulfones when $H_2\,^{18}O$ is used in the preparation of the $H^{18}OF \cdot CH_3CN$ labelled complex.

As previously mentioned, the initial oxidation of a sulfide to a sulfoxide is more easily achieved, and therefore the number of reagents available for this reaction is greater than that available for the sulfide to sulfone oxidation. However, the details of the various routes to sulfoxides will not be discussed here, and the reader is referred to the review by Madesclaire [40].

2.2. Oxidation of Sulfur Compounds with Oxone®

Potassium hydrogen persulfate ($KHSO_5$) is commercially sold as oxone®. It is an inexpensive, air-stable, and easy to handle quaternary mixture of salts containing 2 moles of $KHSO_5$, 1 mole of K_2SO_4 and 1 mole of $KHSO_4$. Trost and Curran showed oxone® in aqueous methanol to be an excellent reagent for the chemoselective oxidation of some phenyl alkyl sulfides to their corresponding sulfones [41]. They also demonstrated the reagent's potential usefulness in the selective oxidation of a sulfide to the corresponding sulfoxide.

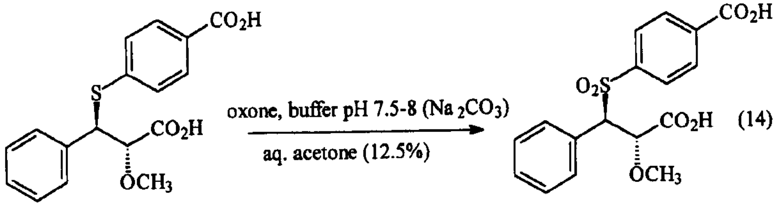
The typical reaction conditions employed were to add a 49.5% $KHSO_5$ solution in water, to a solution of the sulfide in methanol at 0°C. The reaction mixture was allowed to warm to ambient temperature, as it stirred for between 20 mins and 4 hours. The sulfone was recovered by extraction into chloroform, typically in excess of 90% isolated yield. Tlc analysis had indicated that the reaction probably proceeded *via* the intermediate sulfoxide which was indicated by a transient spot exhibiting a greater polarity than both the starting sulfide and sulfone product.

An excess of oxone® was necessary for rapid completion of the oxidation to the sulfone. Oxidation to the sulfoxide was achieved by using an equimolar amount of the oxidant and by maintaining the reaction temperature at 0°C throughout. Although the authors report that the reaction medium is acidic at pH 2–3, and that a buffer can be used to maintain a pH at approx. 5, they do not report if there are any advantages or an increased yield when a buffer was used, although it would naturally be beneficial in oxidations of acid sensitive sulfides.

Further use of oxone® in the selective oxidation of phenyl alkyl sulfides to either sulfones or sulfoxides was achieved in refluxing chloroform or dichloromethane, in the presence of moist alumina as a catalyst [42]. The sulfoxides were obtained when equimolar amounts of the oxidant were used, and the sulfones were obtained on reaction with a three-fold excess of oxone®. No reaction was observed in the absence of the wet alumina catalyst under the same reaction conditions.

The oxone® in 50% aqueous methanol system previously outlined was shown to be unsuitable for the sulfide oxidation step in the synthesis of a peptido leukotriene receptor antagonist **12**, even on the addition of a PTC and with gentle heating (55°C). The oxidation was however dramatically improved by the use of acetone as a co-solvent

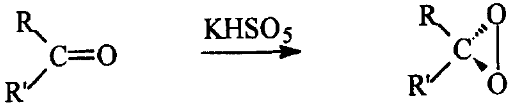
(Eq. (14)) [43].



(14)

12 (96%)

The improved yield of the sulfone was attributed to the probable formation of dimethyldioxirane intermediate and its subsequent role as the oxidising species. It was Murray *et al.* [44] who showed that oxidation on sulfur was possible using dimethyldioxirane **13** ($R = R' = $ Me) generated *in situ* from oxone catalysed decomposition of acetone in the so-called 'caroate' system (Eq. (15)).



(15)

13

They showed that phenyl methyl sulfide was oxidised to phenyl methyl sulfoxide in 98% yield with approx. 1 equivalent of an acetone solution of dimethyldioxirane, at room temperature. Further work by the same group showed that dimethyldioxirane is electrophilic in nature. They investigated this by using competition reactions in the oxidation of a range of *para*-substituted phenyl methyl sulfides and sulfoxides *versus* phenyl methyl sulfide [45]. Plots of the relative rate data against Hammett σ values were used to determine ρ values of -0.77 and -0.76 for the sulfide and sulfoxide oxidations respectively. Both these series of oxidations were seen to be instantaneous and the ρ values calculated from the Hammett linear free energy relationship indicated that the oxidising reagent, dimethyldioxirane, is electrophilic. The small observed difference between the two values indicates that sulfides are slightly more easily oxidised by electrophiles than sulfoxides.

Dioxiranes generated *in situ* from the caroate–ketone system have been used by Colonna and Gaggaro [46] in the enantioselective oxidation of a range of aryl alkyl sulfides to the corresponding sulfoxides by using bovine serum albumin (BSA) as a chiral auxiliary in buffered aqueous solutions of the oxidant. Up to 89% e.e. was observed for the formation of phenyl *i*-propyl sulfoxide and 73% e.e. for phenyl *t*-butyl sulfoxide when acetone or hexafluoroacetone were used as the ketone catalysts. Under the reaction conditions of 4°C with a two-fold excess of the oxidant, only negligible amounts of sulfone ($< 5\%$) were observed.

The mechanism of decomposition of caroate, $KHSO_5$, catalysed by ketones was postulated from the results of labelling experiments involving doubly ^{18}O labelled caroate and unlabelled ketone, or ^{18}O labelled ketone and unlabelled caroate, and from the observation that the catalysed rate of decomposition is first order in $[HSO_5^-]$ and in $[OH^-]$ [47–49]. The labelling experiments confirmed the dioxirane intermediate. The resulting postulated mechanism incorporates the most important observation that the ketone is not used up in the reaction, and is thus catalytic in nature [49].

2.3. Oxidation of 4,4′-dinitrodiphenyl Sulfide with Oxone®

Prior to our work [14] there were no references to the oxidation of diaryl sulfides with oxone® despite the advantages which it has over more traditional reagents, such as potassium permanganate [30, 31] or hydrogen peroxide [28, 29], which have been more frequently used for this transformation. Diaryl sulfides are less easily oxidised than either dialkyl or aryl alkyl sulfides, and those containing electron-withdrawing groups in the aromatic ring would be anticipated to require the strongest reaction conditions or most powerful reagents to afford the transformation.

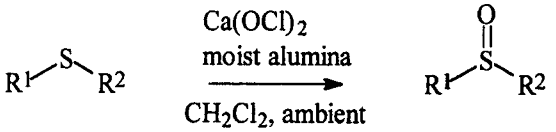
An investigation into the suitability of oxone® as an oxidant in the oxidation of 4,4′-dinitrodiphenyl sulfide was therefore carried out using some of the reaction conditions previously described for the oxidation of aryl alkyl sulfides [41–43] (Tab. VIII).

TABLE VIII Oxidation of 4,4′-dinitrodiphenyl sulfone with oxone®

Amount of oxone®	*Solvent*	*Reaction conditions*	*Isolated yield of sulfone*	*Ref.*
3 equiv.	CH_2Cl_2	4 h/0–25°C	Nil	[42]
3 equiv.	$CHCl_3$	24 h/reflux	45%	[42]
3 equiv.	Acetone	3 h/reflux	73%	[43]

The general procedure was to add a solution of oxone® dissolved in water, to a solution of the sulfide in a solvent. The reaction mixture was stirred vigorously under the conditions shown (Tab. VIII), and the reactions monitored by tlc. In the case where moist alumina was used as a catalyst, this was previously prepared by shaking water and alumina in a flask to obtain a free-flowing homogenous powder. This was then added to the sulfide solution, followed by the aqueous solution of oxone® [14].

Although the use of moist alumina as a catalyst [42] improved the reaction in halogenated solvents, it still gave rise to unsatisfactory yields of sulfone and required a much longer reaction time compared to that in acetone (Tab. VIII). The precise role of the moist alumina is probably as an inorganic support which has also found use as a catalyst in the oxidation of various sulfides to the corresponding sulfoxides with calcium hypochlorite as oxidant (Eq. (16)) [50]. Here the oxidation was also found to be unsuccessful in the absence of the catalyst.



(16)

(R^1 = Ph, R^2 = alkyl, CH_2Cl, $(CH_2)_2OH$, Ph, $PhCH_2$, vinyl, etc.
R^1 = Me, R^2 = $MeOC_6H_4$, ClC_6H_4, $NO_2C_6H_4$, NCC_6H_4, etc.)

The best reaction conditions for the oxidation of 4,4′-dinitrodiphenyl sulfide, was found to be when an excess of oxone® (3 equiv.), dissolved in water, was added to a refluxing solution of the sulfide in acetone. The reaction was complete in approximately 3 hours. Further analysis led to confirmation of the sulfone product by mass spectrometry, which in addition to ^1H and ^{13}C nmr data indicated complete oxidation to the sulfone with no detectable amount of the corresponding sulfoxide or starting material [14].

The great improvement on the reaction when it was carried out in refluxing aqueous acetone could have been due to the better solubility of the 4,4′-dinitrodiphenyl sulfone in acetone than in either chloroform or dichloromethane, or because of the far greater miscibility of acetone with water than halogenated solvents. This would provide a better reaction interface, in which the water soluble oxone® and acetone soluble sulfide could react.

Another possibility that must be considered is the potential presence of dimethyldioxirane as an active oxidising species when acetone is used as solvent. This would be different to the ionic species (HSO_5^-) responsible for oxidation in mixtures of water and inert solvents such as chloroform. Dimethyldioxirane could be formed in the acetone-catalysed decomposition of the oxone®, and could then go on to oxidise the sulfide. This intermediate has been shown to be the active species in a range of oxidations including the oxidation of sulfides to sulfones [44, 45] and is probably responsible for the improved yield of the peptido leukotriene receptor antagonist (**12**) reported by Webb (Eq. (12)) [43]. However, oxidations with *in situ* generated dimethyldioxirane have all been performed in the presence of a buffer to maintain the pH around neutral or slightly alkaline. This is because oxone® is acidic, and the rate of the catalytic decomposition of caroate catalysed by ketones is dependant on $[OH^-]$ and $[HSO_5^-]$ concentrations [47–49].

It seems likely on balance, that the first two explanations of improved solubility and miscibility may well be the reason for the improved yield of 4,4′-dinitrodiphenyl sulfone when acetone was used as the co-solvent. This is further supported by the reported successful oxidations of aryl alkyl sulfides to their corresponding sulfones in good yields when $MeOH/H_2O$ was the solvent system used [41]. Here dimethyldioxirane is not an intermediate and the success of the reaction is probably due to the good miscibility of the two solvents. It is however interesting to note that for each of the oxidations investigated herein, the acetone solution turned pale yellow after about 20 minutes and that dimethyldioxirane can be kept in acetone solution for several days and is reported to be pale yellow in solution, due to its absorption extending from the UV region into the visible at *ca.* 440 nm [48]. This colour sometimes persisted even after work-up and despite the fact that most of the starting materials and products were white.

2.4. Oxidation of Diaryl Sulfides with Oxone® in Aqueous Acetone

The reaction conditions previously outlined, with 3 equivalents of oxone® in refluxing aqueous acetone were subsequently used in the oxidation of several other diaryl sulfides and an aryl benzyl sulfide

TABLE IX Oxidation of diaryl sulfides with oxone® in refluxing aqueous acetone [14]

Substituents	*Reaction time (h)*	*Isolated yield (%)*	*M.P. (°C)*
H	24	89	123–125
NO_2	3	73	267–269
CN	4	92	229–233
OH	4	69	243–244
OMe	4	95	131–136

(Tab. IX) [14]. As can clearly be seen, oxone® proved to be an excellent reagent for the oxidation of all the sulfides investigated. The isolated yields reported are all after a single recrystallisation and the melting points were consistent with the literature values. No partial oxidation to the intermediate sulfoxide was observed for any of these sulfides under the reaction conditions outlined.

It seems probable under the reaction conditions outlined, in the absence of a buffer, that the oxidising species responsible is ionic HSO_5^-. The better yields of sulfone when acetone is used as solvent are therefore attributed to the better solubility of the sulfide in acetone than halogenated solvents rather than to the formation of dimethyldioxirane as the active oxidising species. The sulfones often crystallised out of solution, and were simply collected by filtration. High isolated yields of the pure compounds were obtained after a single recrystallisation from EtOH.

In summary oxone® proved to be an excellent reagent for this oxidation. It afforded high isolated yields, regardless of the functional groups present on the aromatic ring, and the oxidation was even tolerant of the phenolic functionality. In addition to this, oxone® itself has advantages over more traditional reagents used for the oxidation of diaryl sulfides. It is a safe, easy to handle solid which is readily removed in a simple work-up. The advantages in avoiding the use of poisonous transition metal based reagents and catalysts are obvious, from the perspectives of both safety and ease of handling in the laboratory, and with regards to the environmental ramifications of waste disposal.

Acknowledgements

The assistance of Dr. G. A. El-Hiti in editing and correcting this manuscript is gratefully acknowledged. Financial support from

EPSRC and Unilever Research in the form of a CASE award to RLD is also appreciated.

References

[1] Durst, T. (1979). *Comp. Org. Chem.*, **3**, 171.
[2] Cremlyn, R. J., (1996). *An introduction to Organosulfur Chemistry* (Wiley, Chichester), Chap. 4.
[3] Vennstra, G. E. and Zwanenburg, B. (1975). *Synthesis*, S19.
[4] Meek, J. S. and Fowler, J. S. (1968). *J. Org. Chem.*, **33**, 3422.
[5] Mulder, R. S., van Leuse, A. M. and Stratling, O. (1967). *Tetrahedron Lett.*, **32**, 3061.
[6] Srinivasan, K. V., Kumar, S. M. and Ayyangar, N. R. (1992). *Synthesis*, p. 825.
[7] Crandall, J. K. and Pradat, C. (1985). *J. Org. Chem.*, **50**, 1327.
[8] Graybill, B. M. (1967). *J. Org. Chem.*, **32**, 2931.
[9] Sipe, H. J., Clary, D. W. and White, S. B. (1984). *Synthesis*, p. 283.
[10] Ueda, M., Uchiyama, K. and Kano, T. (1984). *Synthesis*, p. 323.
[11] Drews, H., Meyerson, S. and Fields, E. K. (1961). *J. Am. Chem. Soc.*, **83**, 387.
[12] Field, L. (1952). *J. Am. Chem. Soc.*, **74**, 394.
[13] Eaton, P. E., Carlson, G. R. and Lee, J. T. (1973). *J. Org. Chem.*, **38**, 4071.
[14] Ward, R. S., Roberts, D. W. and Diaper, R. L., unpublished results.
[15] Oae, S. (1977). *Organic Chemistry of Sulfur* (Plenum Press, N.Y), Chap. 10.
[16] Truce, W. E. and Vriesen, C. W. (1953). *J. Am. Chem. Soc.*, **75**, 5032.
[17] Olah, G. A., Kobayashi, S. and Nishimura, J. (1973). *J. Am. Chem. Soc.*, **95**, 564.
[18] De Benedetti, P. G., Folli, U., Iarossi, D. and Frassineti, C. (1985). *J. Chem. Soc., Perkin Trans. 2*, p. 1527.
[19] Yoshii, Y., Ito, A., Hirashima, T., Shinkai, S. and Manabe, O. (1988). *J. Chem. Soc., Perkin Trans. 2*, p. 777.
[20] Choudary, B. M., Chowdari, N. S., Kantam, M. L. and Kannan, R. (1999). *Tetrahedron Lett.*, **40**, 2859.
[21] Gilman, H., Beaber, N. J. and Myers, C. H. (1925). *J. Am. Chem. Soc.*, **47**, 2047.
[22] Shiota, Y., Nagai, T. and Tokura, N. (1969). *Tetrahedron*, **25**, 3193.
[23] Baarschers, W. H. (1976). *Can. J. Chem.*, **54**, 3056.
[24] Frye, L. L., Sullivan, E. L., Cusack, K. P. and Funaro, J. M. (1992). *J. Org. Chem.*, **57**, 697.
[25] Hirsch, E., Hunig, S. and Reissig, H.-U. (1982). *Chem. Ber.*, **115**, 3687.
[26] Labadie, S. S. (1989). *J. Org. Chem.*, **54**, 2496.
[27] Fatiadi, A. J. (1987). *Synthesis*, p. 108.
[28] Baker, B. R., Querry, M. V. and Kadish, A. F. (1950). *J. Org. Chem.*, **15**, 402.
[29] Schultz, H. S., Freyermuth, H. B. and Saul, R. B. (1963). *J. Org. Chem.*, **28**, 1140.
[30] Gokel, G. W., Gerdes, H. M. and Dishong, D. M. (1980). *J. Org. Chem.*, **45**, 3634.
[31] Aitken, R. A., Mesher, T. E., Ross, F. C. and Ryan, B. M. (1997). *Synthesis*, p. 787.
[32] Djerassi, C. and Engle, R. R. (1953). *J. Am. Chem. Soc.*, **75**, 3838.
[33] Priebe, W. and Grynkiewicz, G. (1991). *Tetrahedron Lett.*, **32**, 7353.
[34] Kende, S. and Guertin, K. R. (1993). *Tetrahedron Lett.*, **34**, 5369.
[35] Carlsen, P. H. J., Katsuki, T., Martin, V. S. and Sharpless, K. B. (1981). *J. Org. Chem.*, **46**, 3936.
[36] Su, W.-G. (1994). *Tetrahedron Lett.*, **28**, 4955.
[37] Leonard, N. J. and Johnson, C. R. (1962). *J. Org. Chem.*, **27**, 282.
[38] Johnson, C. R. and McCants, D. I. (1964). *J. Am. Chem. Soc.*, **86**, 2935.
[39] Rozen, S. and Bareket, Y. (1994). *Tetrahedron Lett.*, **35**, 2099.
[40] Madesclaire, M. (1986). *Tetrahedron*, **42**, 5459.

[41] Trost, B. M. and Curran, D. P. (1981). *Tetrahedron Lett.*, **22**, 1287.
[42] Greenhalgh, R. P. (1992). *Synlett.*, p. 235.
[43] Webb, K. S. (1994). *Tetrahedron Lett.*, **35**, 3457.
[44] Murray, R. W. and Jeyaraman, R. (1985). *J. Org. Chem.*, **50**, 2847.
[45] Murray, R. W. and Jeyaraman, R. (1987). *J. Org. Chem.*, **52**, 746.
[46] Colonna, S. and Gaggero, N. (1989). *Tetrahedron Lett.*, **30**, 6233.
[47] Edwards, J. O., Pater, R. H., Curci, R. and DiFuria, F. (1979). *Photochem. Photobiol.*, **30**, 63.
[48] Adam, W., Curci, R. and Edwards, J. O. (1989). *Acc. Chem. Res.*, **22**, 205.
[49] Montgommery, R. E. (1974). *J. Am. Chem. Soc.*, **96**, 7820.
[50] Hirano, M., Yakarabe, S., Itoh, S., Clark, J. H. and Morimotoa, T. (1997). *Synthesis*, p. 1161.