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REVIEW

Generation, structure and reactions of sulfenic acid anions

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A comprehensive review of recent chemistry of sulfenate anions is presented. Compound structure, methods of generation and reaction of sulfenates are all addressed. Topical areas including asymmetric alkylation, sulfinyl zinc species and bio-organic mechanisms are covered.

Keywords: Sulfenate; Alkylation; Theoretical chemistry; S−O bond; Sulfenic acid; Sulfur acids

1. Introduction

Sulfenic acids, having the general structure RSOH, are inherently unstable [1, 2]. Nevertheless, persistent effort has led to the isolation of several sulfenic acids [3–11] while numerous other studies have been prompted by the need to elucidate the sulfur chemistry of compounds isolated from plants of the *Allium* genus [12]. Indeed our understanding of the role of sulfenic acids and their derivatives in the chemistry of vegetables such as garlic and onions has matured significantly [12–15].

While sulfenic acids, and their esters and amides have received significant attention and their chemistry has been reviewed [1, 10, 16–18], the attention given to sulfenic acid anions is lagging behind. Although these anions have been known for over 40 years and articles have appeared sporadically, the volume of research accumulated in the last 15–20 years suggests that sulfenates can be useful entities for organic synthesis and are important intermediates in bioorganic transformations. Moreover, only two reviews have been dedicated to this under-explored family of sulfur acid derivatives. One is an unrefereed periodical article [19] while the other offers a concise summary of sulfenate reactions up to 1973 [16]. Hence this review will emphasize contributions since 1973.

Sulfenate anions may be represented in two valence bond forms, **1** and **2** (scheme 1). The most noteworthy difference between these two structures may be the placement of the counterion. The depictions of scheme 1 are generally accepted, and account for the simple substitution chemistry of sulfenates. Specifically, it has been reported that sulfenate anions are

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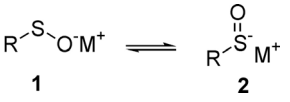
ambident and hence alkylation may occur at either the sulfur or the oxygen [20]. Sulfenates have limited stability in solution and only in rare cases have been isolated. It is often the chemistry of the sulfenates that has been used as a tool to surmise their intermediacy and in many cases their structure. Typically, proof of their existence is inferred from characterization of the sulfoxide that arises from *S*-alkylation of the sulfenate. Treating sulfenates with reactive alkyl halides (*e.g.*, MeI, BnBr) in at least equimolar amounts ensures this outcome.



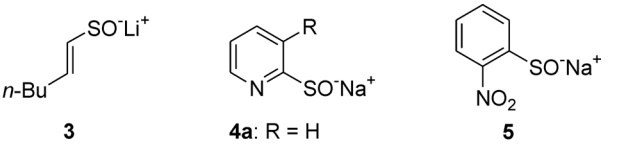
1 **2**

SCHEME 1

In contrast to the usefulness of other sulfur nucleophiles, sulfenates have relatively little synthetic utility. This may be due to their chemical lability [21, 22], but a contributing factor is most certainly that approaches available for their generation are few and, until recently, there has been no single broadly applicable protocol for their synthesis. Several groups have worked to overcome the issues associated with sulfenates [19], and as a result of recent progress, both practically and computationally, have produced a clearer picture of the structure and synthetic value of sulfenates. The present review summarizes advancements made through to early 2004 and will, hopefully, prompt more investigation in the area.

2. Characterization and theoretical studies of sulfenate anions

Although solutions of sulfenates are readily quenched to secure a derivatized end product, only a few examples of characterization of the sulfenate entity exist. Specifically, Schwan determined the ^{1}H NMR of labile lithium sulfenate **3** through its creation in THF-d_8 [23]. Furukawa has described stable heteroatomic sodium sulfenate anions (**4**), which are isolable and characterizable by IR spectroscopy [21].



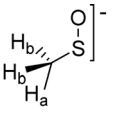
3 **4a**: R = H **4b**: R = TMS **5**

Sulfenate **3**, prepared on an NMR scale by treating *anti*-*n*-butyl thiirane *S*-oxide with solid LiHMDS·Et_2O, has been observed in solution at −78 °C. Vinylic resonances were measured at 6.2 (d) and 5.0 ppm (dt) for the α and β hydrogens, respectively. The chemical shifts are indicative of significant electron donation from the sulfenate to the double bond – much more than that donated by the divalent sulfur of a typical butenyl thioether such as benzyl 1-hexenyl sulfide, which has vinylic proton resonances at 5.9 (d) and 5.7 (dt) ppm [24].

Sulfenates **4** have also been characterized by melting point, elemental analysis and IR spectroscopy [21]. The characteristic S−O stretch is observed between 870 and 890 cm^{-1}, depending on the attached R group [21, 25]. The IR stretching frequency (νSO) for methanesulfenate was calculated (B3LYP/6-31G(d,p)) to be 836 cm^{-1} [26]. As a comparison, the SO stretching frequency in methanesulfenic acid was calculated to be 756 cm^{-1} [26], and 770 cm^{-1} was found experimentally for an azetidinone sulfenic acid [7]. The difference on going from sulfenic acid to its conjugate anion (sulfenate) is consistent with some onset of multiple bond character between the S and O.

Characterization by UV spectroscopy is most common for a single sulfenate. A blue solution consistent with an absorption of $\lambda_{max} = 588$ nm was found to be an attribute of 2-nitrobenzenesulfenate (**5**) in aqueous dioxane [27].

The formation of methanesulfenate (**6**) in the gas-phase by HO^- deprotonation of methanesulfenic acid has been studied by Downard and co-workers [28]. The collisional activation mass spectrum ($M^+ = m/z$ 63) shows the anticipated loss of $^{\bullet}CH_3$, whereas the loss of H_2O is interpreted as an artifact of decomposition of the sulfenic acid precursor. *Ab initio* (MP2/6-31+G(d)//HF/6-31+G(d)) calculations indicate that α-sulfur anion **7** is a higher energy tautomer than a typical sulfenic acid anion. The sulfenate has a bond length of 1.580 Å, which is between that of a single S−O bond (∼1.66 Å) [29] and a double S=O bond (∼1.490 Å). Various other physical data are gathered in table 1.



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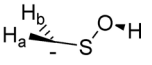

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Table 1. *Ab initio* calculations for the gas-phase methanesulfenate anion **6**.

Bond length (Å)[a]		Bond angle (°)[a]	
H_aC	1.092	$<H_aCS$	109.1
H_bC	1.087	$<H_bCS$	110.7
CS	1.812	<CSO	103.5
SO	1.580	H_aCSO	180.0
		H_bCSO	−60.0

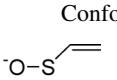
[a]Geometries determined at the HF/6-31 + G(d) level.

Examination of the ion molecule chemistry of methanesulfenate indicates that it has a reactivity between that of HO_2^- and HCO_3^-, making it an oxidizing agent. It can undergo reactions with CS_2 and COS, albeit slowly, and while the electron transfer with sulfur dioxide is surprisingly fast, minor oxidation reactions are observed.

Deprotonation of thiirane *S*-oxides is a proven method for the generation of ethenesulfenate anions through rearrangement chemistry (*vide infra*) [30–33]. In follow-up studies three groups have offered a theoretical analysis related to the rearrangement, and two of these groups have calculated the gas-phase structures of cisoid and transoid ethenesulfenate anions (**8**) not accompanied by counterions. Important structural features are summarized in table 2. The cisoid conformation appears to be slightly more stabilized than the transoid.

The variation of the bond length and bond angle values calculated in these studies does not rigorously define the structure of the sulfenate. Depending on the basis set employed, the C=C bond length may extend beyond the normal alkene length of 1.34 Å, which is consistent with some sulfur to alkene conjugation. Indeed, the HOMO of ethenesulfenate has electron density at O, S and the β-carbon [34]. The S−C bond length is considerably shorter than that found for methanesulfenate (table 1). The broadening of ∠C−S−O is also consistent with electron donation to the alkene. Merrill and co-workers [35] also determined the structure of ethenesulfinate using the MP2(fc)/6-31+G(d,p) basis set. The C=C bond length was slightly shorter (1.341 Å). The S−C bond length was found to be longer (1.814 Å), which is also consistent with reduced sulfur to vinyl conjugation on going from the sulfenate to the sulfinate.

Table 2. Calculated parameters for sulfenate anions.

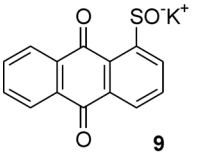
Calculated parameter	Method	Conformation  **8a**	 **8b**	Ref.
Relative energies	RHF/STO-3G*	−19.8	−17.5	34
(kcal mol^{-1})	RHF/3-21+G*	−56.6	−56.5	34
	MP2/3-21+G*	−48.9	−52.0	34
	G2+	−40.00	−32.3	35
∠C−S−O	3-21+G*	104.26	106.54	34
	STO-3G*	110.23	112.43	34
	MP2(fc)/6-31+G(d,p)	106.5	107.5	35
r(C=C) (Å)	3-21+G*	1.3357	1.3334	34
	STO-3G*	1.3379	1.3353	34
	MP2(fc)/6-31+G(d,p)	1.363	1.362	35
r(S−C) (Å)	3-21+G*	1.7554	1.7507	34
	STO-3G*	1.7164	1.7082	34
	MP2(fc)/6-31+G(d,p)	1.733	1.725	35
r(S−O) (Å)	3-21+G*	1.6228	1.6070	34
	STO-3G*	1.5307	1.5257	34
	MP2(fc)/6-31+G(d,p)	1.602	1.587	35

3. Methods of generation

Methods available for the generation of sulfenate anions are by no means numerous, but are slowly increasing in number. The approaches include sulfur oxidation, addition–elimination reactions, ring opening or ring manipulation routes, sigmatropic rearrangements and metal insertion reactions. These techniques have generated alkenesulfenates, arenesulfenates and alkanesulfenate anions. Below are outlined specific methods available for the generation of specific sulfenate anions.

3.1 *Generation of arenesulfenate anions*

Fries' [36] initial discovery of anthraquinone-1-sulfenate (**9**) in 1912 by the alkaline hydrolysis of alkyl sulfenate esters spawned the synthesis of the 1,4-disulfenic acid derivative (**10a**) in 1957 by Bruice and Markiw. Upon isolation, **10a** could be converted into its bifunctional barium, potassium, sodium and lead salts [37]. This was the first example of an isolable disulfenate anion. The contributions of Bruice and Markiw coupled with Jenny's corroborating synthesis [38, 39] of **10a** and of the 1,5-derivative (**10f**) represent important early contributions in arenesulfenate anion chemistry.



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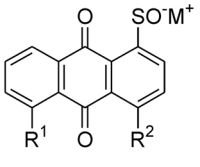
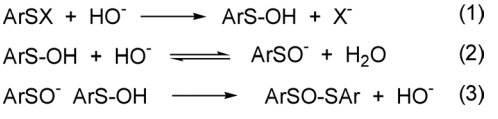


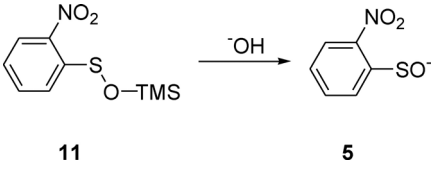
10 a: R^1 = H; R^2 = SOH; M^+ = H
b: R^1 = H; R^2 = SOBa; M^+ = Ba
c: R^1 = H; R^2 = SOK; M^+ = K
d: R^1 = H; R^2 = SONa; M^+ = Na
e: R^1 = H; R^2 = SOPb; M^+ = Pb
f: R^1 = SOK; R^2 = H; M^+ = K

3.1.1 ***Alkaline hydrolysis.*** Methods used for the generation of sulfenate anions were typically very specific and required harsh conditions. Alkaline hydrolysis of arenesulfenate esters was a popular means of creating arenesulfenate anions [22, 27, 40–42]. Kinetic studies performed by Hogg *via* the alkaline hydrolysis of arenesulfenate esters suggested that the sulfenate anion, in equilibrium with its sulfenic acid (equation 2, scheme 2), reacts to produce the thiosulfinate ester (equation 3). This study also revealed the UV maximum, at 588 nm, that was ultimately attributed to the sulfenate anion **5** [27].



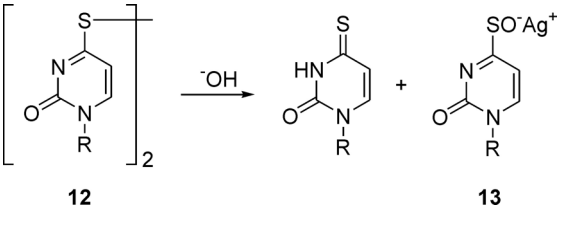
SCHEME 2

Base hydrolysis of trimethylsilyl 2-nitrobenzenesulfenate (**11**) as a source of 2-nitrobenzenesulfenate anion (**5**, scheme 3) was investigated by Davis and Friedman [43]. Treatment of **11** with ethanol–water–sodium hydroxide gave a blue solution, with an absorption at 588 nm, again consistent with the 2-nitrobenzenesulfenate anion (**5**) [27]. The authors demonstrated that the sulfenate could persist in solution for more than 6 h, as exemplified by the blue colour in aprotic media. This was achieved using 18-crown-6 in benzene and employing potassium *tert*-butoxide as base.



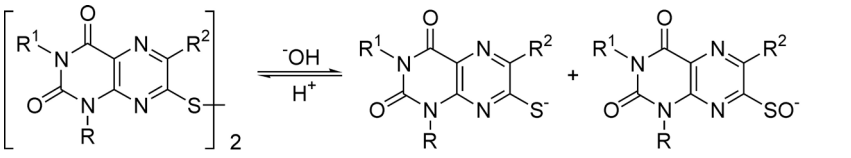
SCHEME 3

Alkaline hydrolysis of bis(4-thiouridine) disulfide (**12**) preformed by Pal and co-workers led to the formation of the corresponding hetarenesulfenate anion **13** (scheme 4) [8]. Of particular note is that sulfenate **13** is stable as its silver salt for 4–6 weeks at temperatures below freezing and may be converted into its sodium salt by passage through a column of Dowex 50 (Na^+).



SCHEME 4

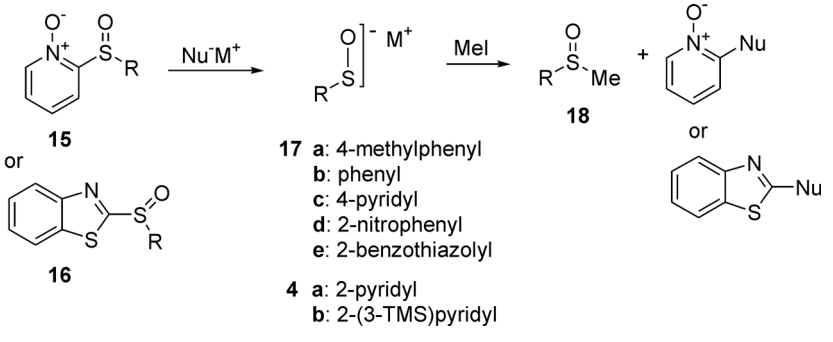
Alkaline hydrolysis of heterocyclic disulfides was also employed by Heckel and Pfleiderer for the formation of lumazine-7-sulfenate anions (**14**, scheme 5) [44]. As per above, and not completely unexpected based on structural similarities, sulfenates **14** can be isolated as their silver salt, a form that tends to be somewhat stable and resistant to disproportionation (see section 4.3).



14 **a**: R = Me; R^1 = Me; R^2 = Me
b: R = Me; R^1 = Me; R^2 = H
c: R = Me; R^1 = H; R^2 = H
d: R = H; R^1 = Me; R^2 = H

SCHEME 5

3.1.2 ***Addition–elimination chemistry.*** Furukawa and co-workers were the first to isolate a stable sodium sulfenate salt *via* an addition–elimination reaction of azaheterocyclic sulfoxides [21]. Sulfenate salts of both 2-pyridyl (**4a**) and 2-(3-trimethylsilyl)pyridyl groups (**4b**) could be isolated and characterized. A small family of (het)arenesulfenates were generated from this sequence by reactions of the azaheterocyclic sulfoxides with either alkoxide or thiolate nucleophiles (scheme 6). Subsequent quenching with methyl iodide afforded the sulfoxide (table 3) [25].



15
or
16

17 **a**: 4-methylphenyl
b: phenyl
c: 4-pyridyl
d: 2-nitrophenyl
e: 2-benzothiazolyl

4 **a**: 2-pyridyl
b: 2-(3-TMS)pyridyl

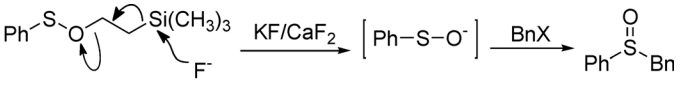
18
or

SCHEME 6

Table 3. Generation and trapping of sulfenate salts *via* the addition–elimination of azaheterocyclic sulfoxides.

Starting heterocycle	R	Nu^-M^+	Yield of sulfoxide **18**(%)
15	4-methylphenyl	EtO^-Na^+	Trace
	phenyl	EtO^-Na^+	54
	2-pyridyl	EtO^-Na^+	94
	4-pyridyl	EtO^-Na^+	53
	2-benzothiazolyl	EtO^-Na^+	55
16	4-methylphenyl	EtO^-Na^+	89
	phenyl	EtO^-Na^+	61
	4-methylphenyl	nBuS$^-$Li$^+$	91
	phenyl	nBuS$^-$Li$^+$	84
	2-pyridyl	nBuS$^-$Li$^+$	87

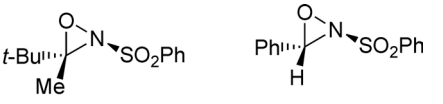
Oida and co-workers provided a very interesting contribution, which relied on a fluoride-induced fragmentation for the generation of an arenesulfenate anion. In 1991, they introduced 2-(trimethylsilyl)ethyl benzenesulfenate (**19**) as a new class of arenesulfenate esters [45]. Reaction of the sulfenate ester with TBAF as a fluoride source proceeds by initial attack of the fluoride ion and a subsequent elimination of the trimethylsilyl group and an ethylene molecule, liberating a benzenesulfenate anion. Although the alkylating agent was present at the outset of the reaction and may react with the sulfur prior to fluoride action, this transformation is nevertheless thought to proceed by way of sulfenate **17b** and the sequence outlined in scheme 7. A follow-up study [46] revealed that the fragmentation-type reaction of benzenesulfenate (**19**) proceeded under completely anhydrous conditions with higher yields and no side-products if KF on CaF_2 was used as the fluoride source and in the presence of benzyl bromide to yield sulfoxide **20**. Notably, if **19** was first reacted with TMSOTf, a sulfinyl *cation* would result [46].



19 **17b** **20**

SCHEME 7

3.1.3 ***Sulfur oxidation.*** In a very simple mindset, sulfenate anions should be deliverable from the corresponding thiolate by means of oxidation. The oxidation of thiolates to sulfenates has proven useful, but only in specialized circumstances [3, 47], and general application of the concept remained under appreciated until work by the Perrio group was published. Those researchers introduced a unique oxaziridine (**21**) for the oxidation of thiols to their corresponding sulfenates [48]. Alkylation of the sulfenate allows for the one-pot conversion of thiols into sulfoxides. Of particular note is the lack of side-products, *i.e.*, neither disulfide formation nor *O*-alkylation product is observed. Additionally, the requisite temperature is much lower than for other oxaziridine-mediated oxidations. A few examples are summarized in table 4. Interestingly, when the traditional Davis reagent (**22**) was used, the transfer of two oxygens occurred uncontrollably, affording the arenesulfinate anion, and ultimately a sulfone after alkylation [49, 50].



21 **22**

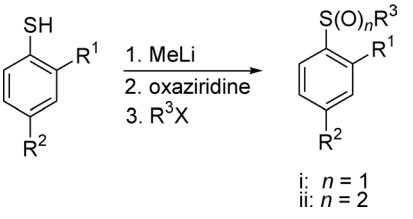
Although this chemistry is interesting and unequivocally influential to sulfenate chemistry, alkanethiols do not participate in the same chemistry, as evidenced by the lack of isolation of any of the expected sulfoxides.

3.2 *Generation of 1-alkenesulfenate anions*

In the realm of sulfenate anion chemistry, the generation and formation of alkenesulfenate anions is comparatively common. Several reports outline the liberation of 1-alkenesulfenate anions, which in turn have served as useful as precursors to 1-alkenyl sulfoxides [30–32, 51–54], 1-alkenesulfenamides [55, 56], 1-alkenesulfonamides [56] and silyl protected enethiols [57].

3.2.1 ***Ring manipulation.*** The Maccagnani group reported the discovery of 1-alkenesulfenate anions (α, β-unsaturated sulfenates) from the treatment of thiirane *S*-oxides with lithium bases [30, 31]. Reactions of diastereomerically pure *cis*-stilbene thiirane *S*-oxide (**24**) and the corresponding *trans*-compound (**25**) with lithium bases afforded results that indicated

Table 4. Dependence on oxaziridine of sulfenate and sulfinate generation and alkylation.



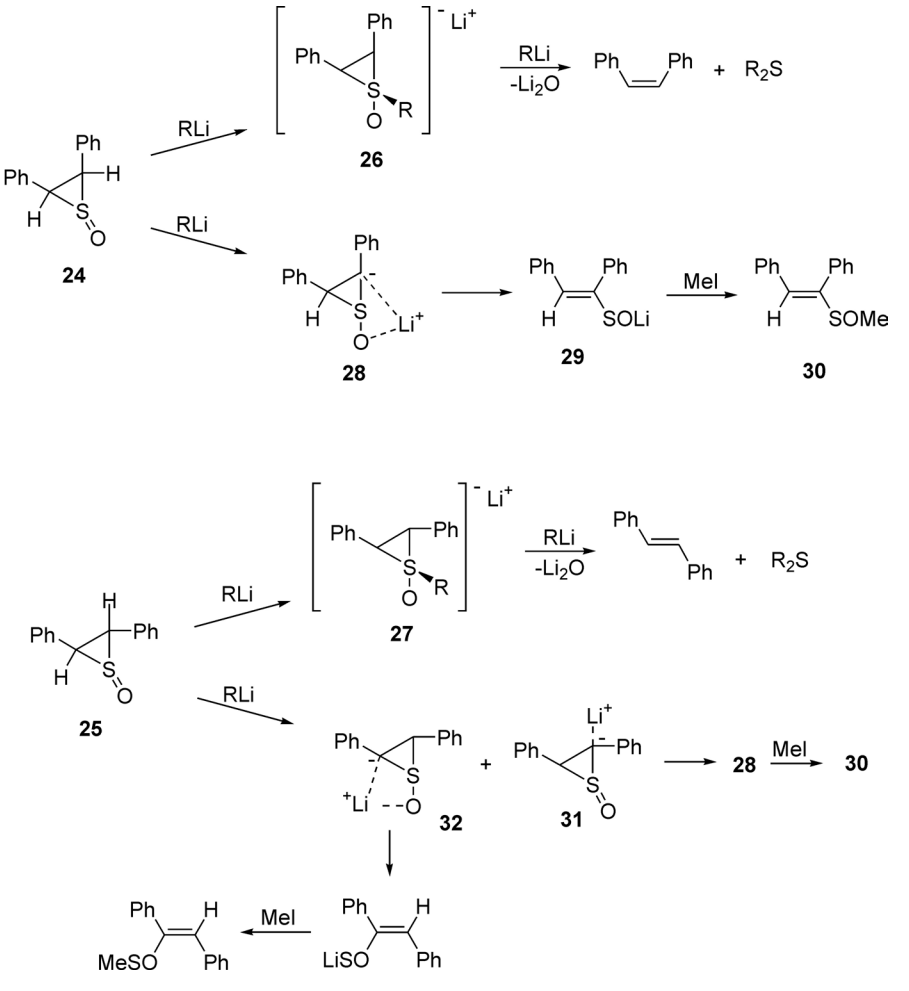
			Yield (%)	
R^1	R^2	R^3	Sulfoxide i *via* **21**	Sulfone ii *via* **22**
H	H	Me	89	75
H	H	Et	83	75
H	H	Bn	79	85
H	SEt	Me	71	71

a stereospecific desulfinylation for both stereoisomers, whereas the ring-opening reaction was only stereospecific for the *cis* compound. Intermediates **26** and **27** are held accountable for the desulfurization reaction, a process that requires reaction with an additional equivalent of base and affords olefinic and sulfide products (scheme 8) [30].

In the mechanistic analysis, thiirane *S*-oxide **24** succumbs to deprotonation from the less hindered side of the molecule to give carbanion **28**, which is stabilized by coordination to the lithium cation and the *syn* sulfinyl oxygen. Intermediate **28** can then rearrange to sulfenate **29**, which after alkylation gives vinyl sulfoxide **30**. Because thiirane *S*-oxide **25** is hindered on both faces, deprotonation yields of vinyl sulfoxide are attenuated. Formation of **30** from **25** is explained through formation of carbanion **31**, resulting from abstraction of the proton that is *anti* with respect to the sulfinyl oxygen. Inversion of **31** into **28** then follows and is driven by the now possible oxygen coordination with the lithium cation [58]. Deprotonation of the other hydrogen of **25** offers anion **32**, which already has the lithium counterion stabilized by the oxygen. Stereoselective ring opening of **32** and quenching gives the Z-vinylic sulfoxide. Attack at sulfur is promoted by typical organolithium species, including *n*BuLi, PhLi, [30, 31] MeLi and Grignard agents but amide bases and MeLi–LiBr complex favour exclusive attack at hydrogen [59].

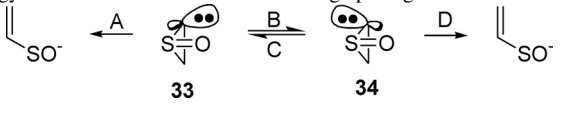
Three computational studies pertaining to this ring opening have been published. The initial one by Maccagnani and co-workers [34] using the 3-21+G* basis set, but without incorporating a counterion, found that the *syn* anion (**33**) and the *anti* anion (**34**) of thiirane *S*-oxide are comparable in energy and that ring opening *via* the *syn* anion is faster (table 5). The **34** to **33** barrier is slightly lower than the *anti* ring opening – consistent with the observed experimental results of scheme 8. The ring opening is suggested to be a conrotatory process (table 5) [34].

Refvik *et al*., working at the 6-31+G(d) level and incorporating a lithium counterion [32], found that **33** was 27.3 kcal mol^{-1} lower in energy than **34**. Anion inversion of **34** into **33** would be driven by the large energy benefit, but would require separation, then recombination of the lithium. Kass and co-workers [35], using the G2+ method without any counterion, found energies for **33/34** ring opening and inversion comparable to those previously found [34], although some of the calculated structures differed. Kass and co-workers also determined the barrier for ring opening of mono-anions of thiirane and thiirane *S*,*S*-dioxide and found them to be higher than that required for ring opening of **33**. Gas-phase theoretical analyses of 1-alkenesulfenate anions have also been performed by Kass and co-workers [35]. Theoretical and experimental proton affinities of those anions and other related sulfur acids are summarized



SCHEME 8

Table 5. Energy barriers for interconversions and ring openings of anions of thiirane *S*-oxide.



Computational method	Ref.	w/Li^+	Barriers of reaction pathways (kcal mol^{-1})			
			A	B	C	D
MP2/3-21+G*	34	N	0.5	7.3	7.6	8.1
6-31+G(d)	32	Y	–	>27.3	–	–
G2+	35	N	3.7	7.1	5.5	11.5

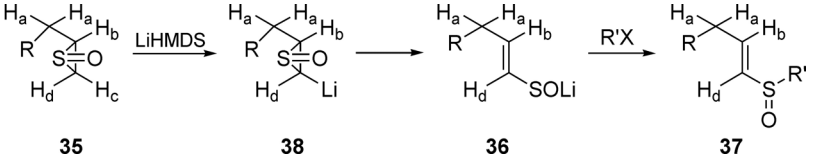
in table 6. The data allows one to evaluate the trends in the gas-phase acidity of the various vinylic sulfur species. 1-Alkenesulfinic acids are most acidic, followed by vinyl thiols and 1-alkenesulfenic acids.

Table 6. Theoretical and experimental proton affinities for vinyl sulfur acid anions.

Species	Theoretical[a]	Experimental
Vinyl thiolate	344.9	348 ± 3
cisoid-1-Alkenesulfenate	349.0	–
transoid-1-Alkenesulfenate	350.5	354 ± 3
1-Alkenesulfinate	332.1	–

[a]Obtained at the G2+ level.

From a practical perspective, examination of the monoalkyl-substituted thiirane *S*-oxide **35** (scheme 9) reveals that, although sulfur may be a site of attack [30], there are also three acidic α hydrogens to the sulfinyl unit available for deprotonation (H_b, H_c, H_d). Hydrogens on the alkyl chain (H_a) may also be acidic because they will aid in ring strain relief once deprotonated and concomitant formation of an allylic sulfenate occurs. Despite the apparent lability of thiirane *S*-oxides, the Schwan group revealed that weaker silazide bases gave clean and selective conversion into the α, β-unsaturated sulfenate (**36**), as evidenced by the isolation of the resulting sulfoxide (**37**) [32, 51]. Lithium hexamethyldisilazide was shown to be selective for the hydrogen that is *syn* to the oxygen and *anti* to the alkyl group (H_c), with some results shown in table 7 [32]. Mechanistically, lithiated species **38** rearranges stereoselectively to sulfenate **36**, which adopts the *trans* conformation exclusively. This hypothesis is supported by the deuterium labeling experiment depicted as the last entry in table 7. Treatment of **39** ($R^1 = n$Bu; R^2 = H; R^3 = D) with LiHMDS afforded only deuterium-free sulfoxide **40** ($R^1 = n$Bu; R^2 = H) in 77% yield after alkylation of the sulfenate. No other product such as **40** ($R^1 = n$Bu; R^2 = D) was observed. Thus, hydrogen removal evidently occurs exclusively at the deuterium followed by the stereoselective conversion into *E*-sulfenate **36** (R = *n*-propyl).



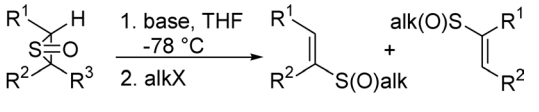
SCHEME 9

The theoretical work by Refvik and co-workers introduced above is consistent with the practical results [32]. The calculations show that lithiated thiirane *S*-oxides possessing the metal *syn* to the oxygen and *anti* to the substituent are the lowest energy species and that the lithium–oxygen interaction is beneficial by 27–30 kcal mol^{-1}.

Although typical organolithium reagents (*i.e.* BuLi, MeLi, PhLi) have a propensity for attack at sulfur, the MeLi–LiBr complex has given results comparative to the silazide bases without competitive attack at sulfur [59]. The discovery that bases such as LDA and LiHMDS participate in exclusive attack at the hydrogens of thiirane *S*-oxides prompted others to re-evaluate similar chemistry with thiirane *S*,*S*-dioxides. Indeed, Simpkins and co-workers found that deprotonation of thiirane *S*,*S*-dioxides with LDA brought about comparable rearrangement chemistry, affording 1-alkenesulfinates [60, 61].

Table 7. Generation and capture of *trans*-substituted ethenesulfenates (scheme 10).

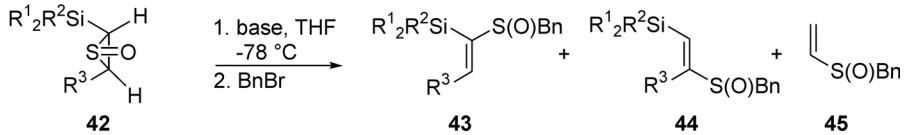
				Products (% yield)	
R^1	R^2	R^3	Base	**40**	**41**
H	H	H	NaHMDS	80	–
*n*Bu	H	H	LiHMDS	75	11
*n*Bu	H	H	LDA	70	–
$nC_{11}H_{23}$	H	H	LiHMDS	79	–
3-butenyl	H	H	LiHMDS	75	–
cC_6H_{11}	H	H	NaHMDS	68	–
$(i\text{Pr})_3SiCH_2$	H	H	LiHMDS	60	–
Et	Et	H	LDA	66	–
$-(CH_2)_4-$	H	H	LDA	75	24
$PhOCH_2$	H	H	NaHMDS	43	13
Ph	H	H	LDA	22	15
Ph	H	H	LiHMDS	29	–
*n*Bu	H	D	LiHMDS	77	



39 **40** **41**

SCHEME 10

Due to the success of the alkyl-substituted thiirane *S*-oxides, a family of silylthiirane *S*-oxides (**42**) was examined to determine the effect of the silyl group in the heterocyclic ring. Thus, presumably due to the increased acidity of the hydrogens α to the silyl group, LiHMDS gave exclusive geminal deprotonation, whereas LDA gave a mixture of products where trans deprotonation was favoured (table 8). With Na- and KHMDS, mixtures were contaminated with benzyl vinyl sulfoxide, which presumably resulted from protiodesilylation of benzyl 1-(trimethylsilyl)ethenyl sulfoxide in solution after addition of benzyl bromide [32].



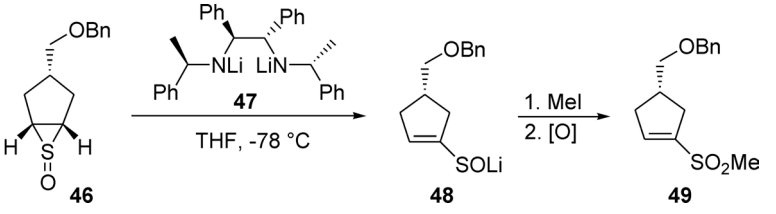
42 **43** **44** **45**

SCHEME 11

The application of chiral lithium amide bases led to the discovery of a desymmetrization reaction of prochiral ring-fused thiirane *S*-oxides (**46**) by the Simpkins group [54]. Reaction of fused thiirane *S*-oxide **46** with chiral base **47** affords stereoselective deprotonation to sulfenate **48**, which, after alkylation and oxidation for ease of ee analysis, led to alkenyl sulfone **49** in 85–88% ee (scheme 12) [53]. Examination of thiirane *S*-oxides **50** and **51** under the chiral base conditions afforded alkenyl sulfoxides in 72% (sulfone: ee 85%) and 82% (sulfone: typical ee 65%), respectively. This chiral base transformation has the capacity to be particularly useful for the synthesis of non-racemic alkenyl sulfoxides.

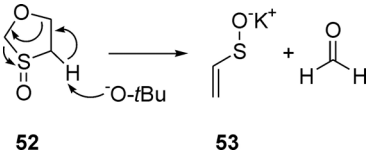
Table 8. Generation and capture of silylated sulfenates with benzyl bromide (scheme 11).

			Products (% yield)		
$R^1_2R^2$	R^3	Base	**43**	**44**	**45**
Et_3	H	LDA	18	49	–
Et_3	H	LiHMDS	58	–	–
Et_3	H	NaHMDS	59	–	3
Et_3	H	KHMDS	36	–	15
Me_3	H	LiHMDS	35	–	–
Ph_3	H	LiHMDS	36	–	–
Me_3	*n*Bu	LDA	58	12	–
Me_3	*n*Bu	LiHMDS	57	–	–
Me_2tBu	*n*Bu	LDA	26	29	–
Me_2tBu	*n*Bu	LiHMDS	54	–	–



SCHEME 12

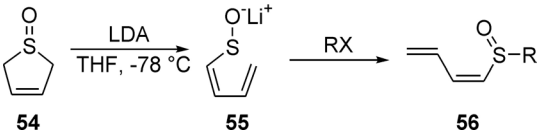
Schank and co-workers created a vinyl sulfenate by virtue of a cyclofragmentation reaction [62]. Deprotonation of 1,3-oxathiolane-3-monoxide (**52**) with potassium *tert*-butoxide produced a violent reaction whereby formaldehyde and vinyl sulfenate (**53**) were concomitantly produced (scheme 13). The sulfoxide resulting from quenching **53** was obtained in only 18% yield.



SCHEME 13

Dienesulfenates are attainable through a ring-opening reaction of 2,5-dihydrothiophene-1-oxide (**54**) studied by Crumbie and Ridley [52]. Treatment of **54** with LDA in THF at −78 °C led to the formation of sulfenate **55** and sulfoxide **56** eventuates upon quenching of the sulfenate

with a reactive alkyl halide (scheme 14). In an exaggerated example of how sulfenates tend to be unstable and labile, if this reaction is carried out at temperatures above −78 °C or if the time delay between generation of the sulfenate and addition of the alkylating agent exceeds 3 s, a large decrease in yield was observed. Additionally, as exemplified in table 9, satisfactory yields are only observed with very reactive alkyl halides. More recently, the analogous ring-opening of substituted sulfolenes has been reported and the intermediate dienesulfinate anions were converted into a library of butadienesulfonyl chlorides [63].



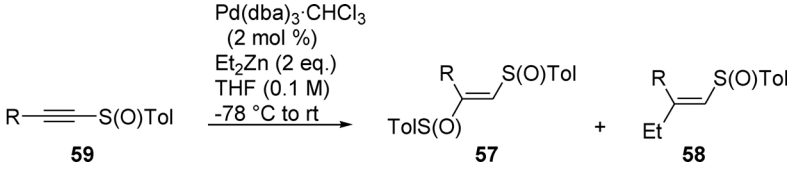
SCHEME 14

Table 9. Effect of alkylating agent in the quenching of sulfenate **55**.

RX	Yield (%)
MeI	49
EtI	8
MeCH(I)Me	0[a]
BnI	21
BnBr	0
BnCl	0
I-CH_2COMe	31
Br-CH_2COMe	0
Cl-CH_2COMe	0
I-CH_2CO_2Et	76
Br-CH_2CO_2Et	53
Br-CH_2COPh	55
4-Br-$CH_2COC_6H_4Br$	65

[a]Polymeric products observed.

3.2.2 ***Metal insertion reactions.*** Straying from classical organic mechanisms, Tanaka and co-workers executed a Pd-catalyzed sulfinylzincation of activated alkynes using 1-alkynyl sulfoxides as a sulfinyl source. The reaction requires Et_2Zn in the presence of a Pd(II) or Pd(0) complex and a zinc sulfenate is suggested as a reaction intermediate [64]. Vinylic sulfoxides **57** and **58** result from the addition of the zinc sulfenate to the alkyne (**59**) with high *syn*-selectivity – a valuable outcome since thiolate Michael additions to alkynes usually offer the *anti*-adduct. The mild and neutral conditions of the reaction tolerate many functional groups. With only a 2% molar catalyst loading, the yields of the reaction generally tend to be quite good (table 10).



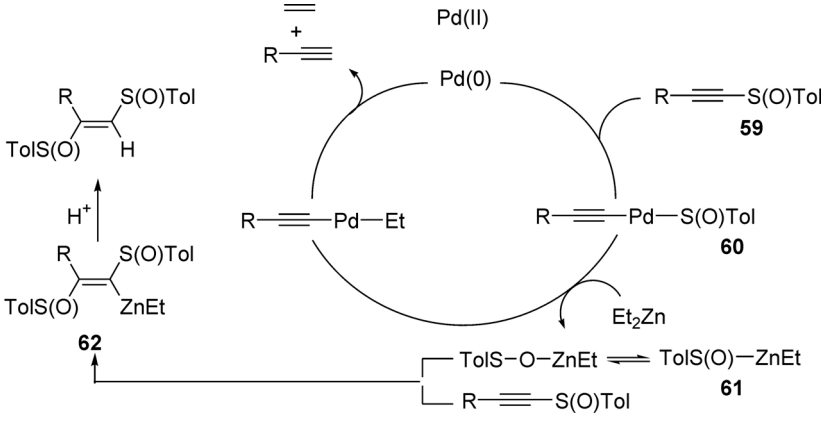
SCHEME 15

Table 10. Pd-Catalyzed sulfinylzincation of 1-alkynyl sulfoxides (scheme 15).

			Yield (%)	
Substrate	R	Time (h)	**57**	**58**
59a	$TBSO(CH_2)_2$	1.5	88	0
59b	$AcO(CH_2)_2$	1.5	82	0
59c	$I(CH_2)_2$	1.5	97	0
59d	H	0.5	24[a]	33[b]

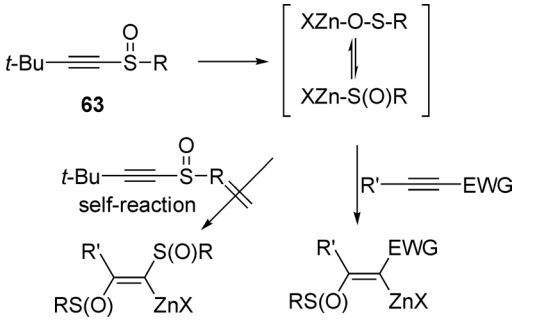
[a]Single diastereomeric isomer. [b]2:1 ratio of E/Z isomers.

The authors remain uncommitted toward any one particular reaction mechanism to account for their results. One mechanistic possibility is offered in scheme 16 wherein oxidative addition of the 1-alkynyl sulfoxide to the Pd(0) complex instigates the reaction generating **60**. It is hypothesized that zinc sulfenate **61** then results from transmetalation of **60** with Et_2Zn. Sulfinylzincation of sulfenate **61** with a second equivalent of 1-alkynyl sulfoxide affords *bis*-sulfinyl vinylzinc species **62**.



SCHEME 16

The reaction as presented in scheme 16 requires alkyne **59** to act as both the source of the zinc sulfenate and as the Michael acceptor. The synthetic usefulness of the reaction may well be expanded if the self-reaction of the zinc sulfenate with the 1-alkynyl sulfoxide could be suppressed and if the sulfenate was trapped efficiently with another activated alkyne. The



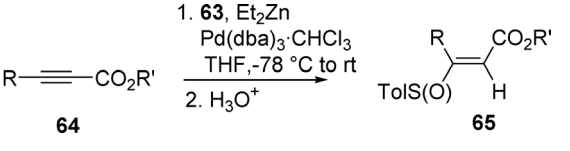
SCHEME 17

self-reaction of *t*Bu substituted alkene **63** (scheme 17) is slow and hence **63** was examined as the sulfinylating agent for the sulfinylzincation of 1-alkynoates (**64**). The result was a dramatic increase in the yields of the resulting vinyl sulfoxide (table 11) [65].

Table 11. Pd-catalyzed sulfinylzincation of 1-alkynoates (scheme 18).[a]

Substrate	R	R′	Yield of **65** (%)
64a	H	Me	87
64b	Me	Et	62
64c	CH_2OBn	Me	100
64c	CH_2OBn	Me	92[b]
64d	CH_2OAc	Me	97
64e	CH_2OTBS	Me	93
64f	CH_2CH_2Bn	Me	48
64g	$(CH_2)_2OBn$	Me	57
64h	$(CH_2)_3OBn$	Me	48
64i	CH_2SBn	Me	98
64i	CH_2SBn	Me	83[b]
64j	$CH_2N(Me)Bn$	Me	98
64j	$CH_2N(Me)Bn$	Me	68[b]

[a]Based on 10 equiv. of substrate unless otherwise noted. [b]2 equiv. of substrate.

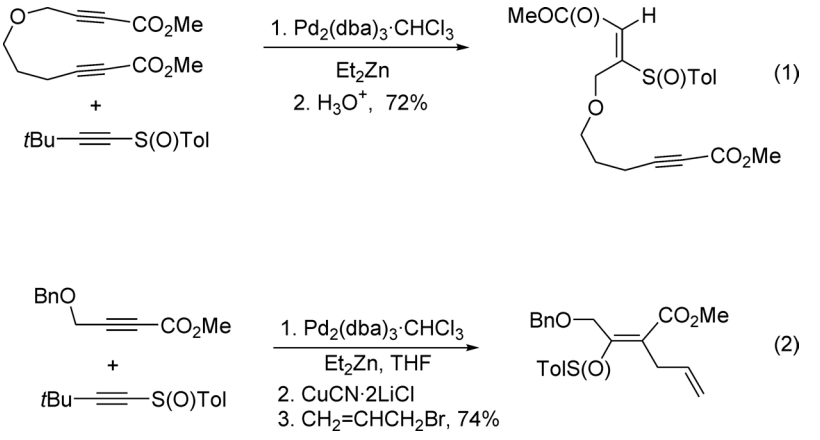


SCHEME 18

With substrates possessing a heteroatom in the δ-position, a particularly noteworthy increase in the yield is hypothesized to be due to coordination of the heteroatom in the substrate to the zinc of the sulfenate. Although the efficacy of the heteroatom differs, reducing in the order O > S > NMe, this is nonetheless an important influence on the zinc sulfenate. The heteroatom may play a co-ordinative role in stabilizing the transition state for the addition reaction. The directing role of an oxygen for instance is demonstrated in scheme 19 (equation 1) [65].

The reaction is not limited to toluenesulfenates. Several zinc arenesulfenates could be generated, as well as methane- and 3-butynesulfenate. Although the products presented herein all represent the *syn* addition of a zinc toluenesulfenate and a hydrogen across a triple bond, Maezaki and co-workers also showed that the intermediate vinyl zinc could be alkylated or acylated after conversion into a cuprate. The result is a tetrasubstituted olefin as in scheme 19 (equation 2) [65]. Finally, the sulfinylzincation protocol has also been successfully applied in intramolecular fashion for the formation of sulfur-containing heterocycles [66] and in an asymmetric manner successfully targeting chiral vinylic sulfoxides [67].

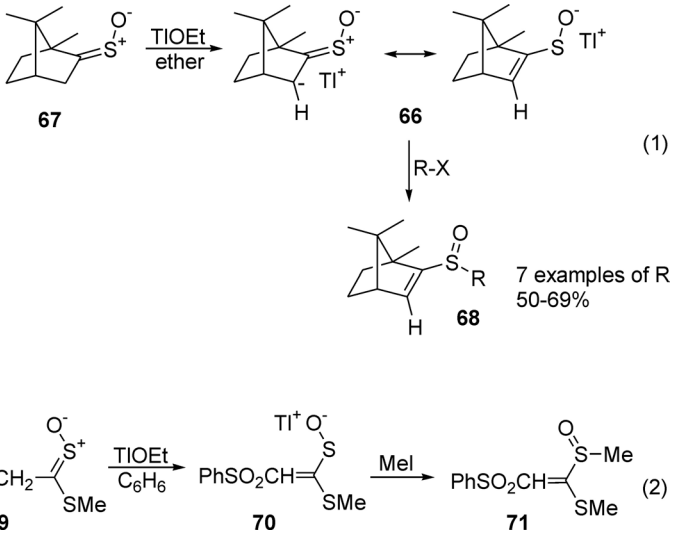
Many researchers have suggested that the counterion of a sulfenate is coordinated to the oxygen (structure **1**, scheme 1). Having zinc as a counterion for a sulfenate raises the question of whether the zinc is nearest the oxygen or the sulfur. Maezaki *et al*. do not make a commitment for either possibility, but do consider the sulfinyl zinc structure (*e.g.*, **2**, M = Zn) as a viable possibility [65].



SCHEME 19

3.2.3 ***Deprotonation of sulfines.*** A carbanionic centre α to a sulfine can share negative charge with the sulfinyl group giving the substrate sulfenate character (*e.g.*, **66**, scheme 20, equation 1). Veenstra and Zwanenburg have demonstrated that the appropriate α-carbanionic sulfines are accessible by way of deprotonation and that two structural types are responsive to this chemistry [68]. Specifically, when thallium(I) ethoxide (TlOEt) is used as a base, thiocamphor *S*-oxide (**67**) is cleanly deprotonated, giving rise to sulfenate **66**. The sulfenate was quenched with various alkylating agents, offering a collection of α, β-unsaturated sulfoxides (**68**). The authors report that the thallium sulfenate precipitates from the ether solution at room temperature.

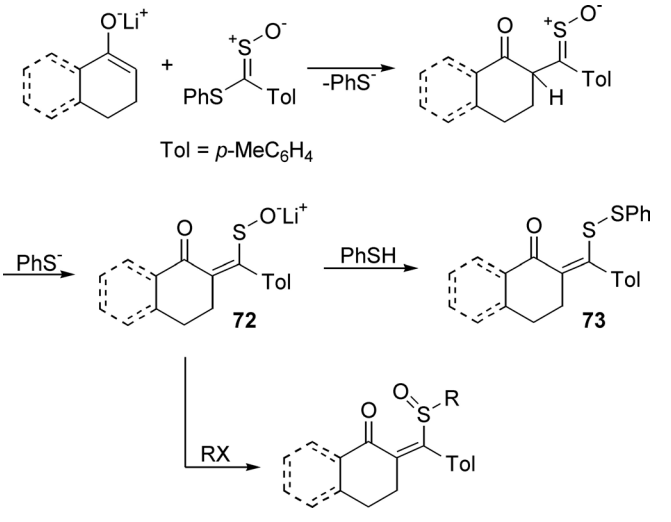
In an additional example, the TlOEt deprotonation of sulfone **69** gave isolable sulfenate **70**, which was subsequently exposed to methyl iodide to afford sulfoxide **71** as a mixture of double bond isomers (scheme 20, equation 2). The use of other bases again proved unsuccessful, although the deployment of Et_3N followed by MeI gave the sulfanyl form of **71** [69].



SCHEME 20

3.2.4 ***Nucleophilic addition to sulfines.*** Sulfenate species similar to **66** and **70** can be generated as a result of the addition of lithium enolates to selected sulfines [70]. As shown in

scheme 21, a sequence of enolate addition, thiolate elimination and thiolate deprotonation gives sulfenates **72**. If left unperturbed the reaction eventually produced disulfides **73**, a process assumed to proceed by thiol attack of sulfenates **72**. Evidence for sulfenates **72** was found by quenching the mixtures with MeI or $PhCH_2Br$. Yields of vinylic sulfoxide reached 70% [70].

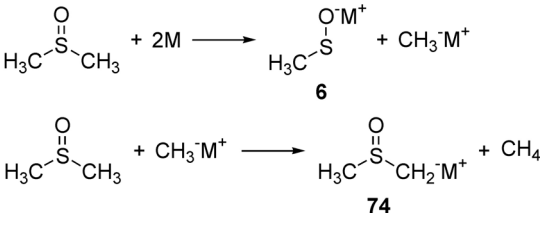


SCHEME 21

3.3 *Generation of alkanesulfenate anions*

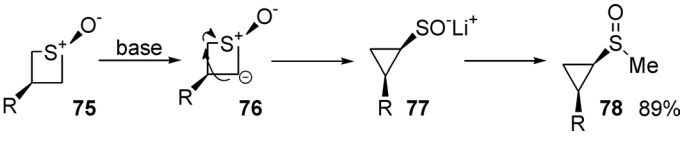
Shelton and Davis outlined the first discovery of an aliphatic sulfenic acid in 1967 [71], and later that year Danehy and Hunter suggested the intermediacy of sulfenate anions as part of a mechanism for the hydrolysis of disulfides [72]. Only later did synthetically viable liberations of sulfenates emerge. As outlined below, those studies were often specific examples that lack general applications.

3.3.1 ***Reducing metal reactions.*** Methanesulfenate was first generated in solution by O'Connor and Lyness by the reaction of either sodium or potassium metal with dimethyl sulfoxide. The harsh reducing metal conditions afford methanesulfenate (**6**) alongside a dimsyl anion (**74**) [73]. Although synthetically quite facile (scheme 22), this protocol suffers because the dimsyl anion is a more potent nucleophile than methanesulfenate and can undergo substitution and addition reactions. Consequently, 2 equiv. of electrophile are required and the reactivity of the dimsyl anion must first be negated for the sulfenate to have any synthetic utility. Moreover, a problem of separation arises since the products of alkylation will be two methyl sulfoxides differing by only one methylene unit in the group opposite the methyl. Fascinating is the authors' claim that **6** is stable in solution at room temperature for several days, a finding that other chemists synthesizing different sulfenates have not observed.

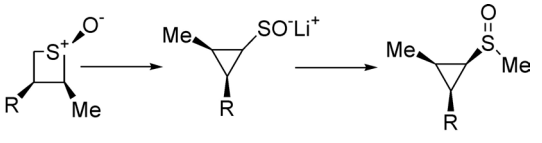


SCHEME 22

3.3.2 ***Ring manipulation.*** A stereospecific anionic ring contraction has been applied by Jones for the formation of cyclopropanesulfenates [74]. Deprotonation of **75** α to the sulfinyl unit of 3-alkylthietane 1-oxides with a lithium amide base affords intermediate **76**, which upon rearrangement affords cyclopropanesulfenate **77**, and after alkylation with methyl iodide affords sulfoxide **78** (scheme 23). For the 2,3-dialkylthietane *S*-oxides (**79**), the ring contraction was found to occur regiospecifically if the sulfinyl oxygen was *cis* to the 2-methyl group in the thietane *S*-oxide (scheme 24).

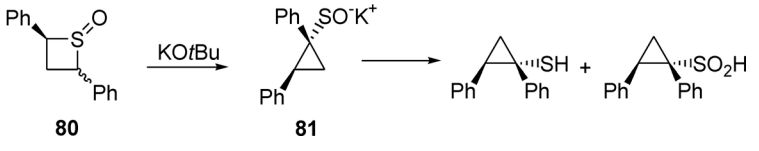


SCHEME 23



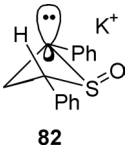
SCHEME 24

Cyclopropanesulfenate was first observed as an intermediate in the stereoselective rearrangement of 2,4-diphenylthietane oxides (**80**) [75]. Treatment of either *cis*- or *trans*-2,4-diphenylthietane 1-oxide with potassium *tert*-butoxide in DMF yielded *cis*-1,2-diphenylcyclopropanesulfenate (**81**) as a probable intermediate. Under the experimental conditions, **81** underwent disproportionation to the corresponding sulfinic acid and mercaptan (scheme 25).



SCHEME 25

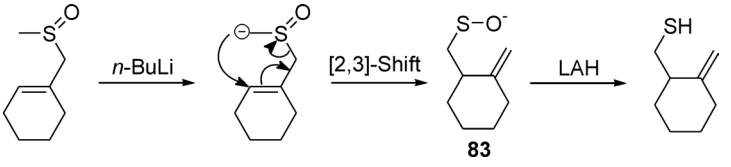
Mechanistically, it was postulated that the hydrogen lying between the oxygen of the sulfoxide and the phenyl group is preferentially exchanged. This in turn would lead to the most configurationally stable anion (**82**) where both phenyl groups are *pseudo*-equatorial and the oxygen is close to the potassium cation.



82

3.3.3 ***Sigmatropic rearrangements.*** A base-mediated transformation of allyl sulfinyl carbanions has been used by the Fokin group to generate homoallyl sulfenate anions *via* a [2,3]-sigmatropic rearrangement (*e.g.*, **83**, scheme 26) [76, 77]. The reaction represents a rare form

of a thia-Wittig rearrangement [78, 79] in that the sulfur is oxygenated. Subsequent reduction of the sulfenate anion with LAH affords δ-unsaturated thiols. Several examples were reported, with yields of thiols ranging from 7 to 73%.

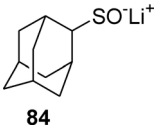


83

SCHEME 26

Using DFT calculations performed with the B3LYP/6-31+G* basis set, it was learned that the rearrangements are concerted and highly exothermic, with a barrier for rearrangement of the free carbanion of only 0.5–3 kcal mol^{-1}. Complexation with a lithium counterion increases the barrier to 21–23 kcal mol^{-1} [77].

3.3.4 ***Addition–elimination.*** As mentioned previously, an addition–elimination reaction of azaheterocyclic sulfoxides was used as an approach for the generation of arenesulfenate anions (section 3.1.2). This method was also employed to generate the 2-adamantanesulfenate anion (**84**); however, it was trapped as its methyl sulfoxide in only 21% yield [25].

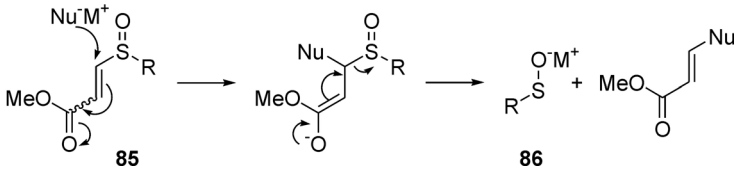


84

3.4 *A specific route to non-specific sulfenate anions*

As evidenced so far, there seems to be a growing number of methods available for the creation of sulfenate anions, but until recently there lacked a general procedure giving rise to a variety of sulfenates, both arene- and alkane-, with a varied selection of substituents on sulfur.

Recently, O'Donnell and Schwan [80] introduced methyl β-sulfinylacrylate esters (**85**) as a source of sulfenate anions. Treatment of acrylates **85** with a nucleophile is believed to involve a Michael-type addition β to the carboxylate unit and then release of the sulfinyl moiety as a sulfenate anion (scheme 27).



85 **86**

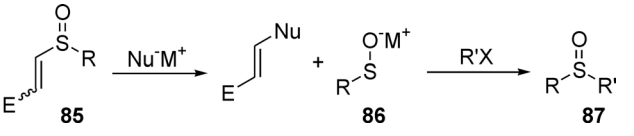
SCHEME 27

The requisite starting sulfoxide **85** is readily prepared by treatment of methyl propiolate with the desired thiol (aromatic or aliphatic) under basic conditions with subsequent oxidation. Although a mixture of E/Z isomers is obtained in each case, the configuration is not critical to the outcome of the subsequent sulfenate-generating reaction. After nucleophilic-induced liberation of sulfenate **86**, quenching with an alkyl halide affords its corresponding sulfoxide. Yields of selected systems are outlined in table 12 [80]. Note that both alkoxide and thiolate

nucleophiles facilitate generation of the sulfenate. It is postulated that sodium methoxide may liberate sulfenate by attack at a hydrogen α to the ester to execute an *E*2 reaction mechanism. The methoxide may also deprotonate alkyl hydrogens α to the sulfinyl unit, thus deceasing the yields slightly.

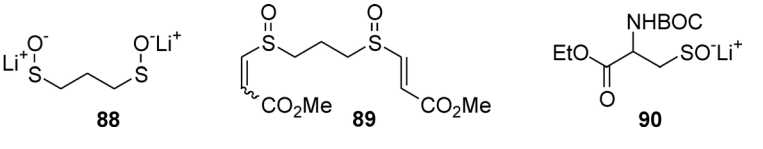
Table 12. Addition-elimination of β-sulfinyl acrylate esters for the generation of sulfenate anions with subsequent quenching to the sulfoxide (scheme 28).

R	Nu^-M^+	R′X	Yield of **87** (%)
p-Tol	MeO^-Na^+	BnBr	84
p-MeC(O)NHC$_6$H$_4$		BnBr	50
n-C$_6$H$_{13}$		BnBr	77
n-C$_6$H$_{13}$		MeI	83
n-C$_{16}$H$_{33}$		BnBr	61
n-C$_{16}$H$_{33}$		MeI	63
c-C$_6$H$_{11}$		BnBr	65
p-Tol	*c*-C$_6$H$_{11}$O$^-$Li$^+$	BnBr	85
n-C$_6$H$_{13}$		BnBr	85
n-C$_{16}$H$_{33}$		BnBr	76
Bn	*c*-C$_6$H$_{11}$S$^-$Li$^+$	BnBr	75
Me		BnBr	62



SCHEME 28

In the same paper, the sulfoxide derived from double benzylation of *bis* sulfenate **88** was isolated in 74% yield. Starting substrate **89** was treated with 2 equiv. of *c*-C$_6$H$_{11}$S$^-$Li$^+$ followed by 2 equiv. of PhCH$_2$Br. In addition, cysteine derivative **90** could be alkylated with PhCH$_2$Br, affording a diastereomeric mixture of benzyl sulfoxides in 46% yield. Remarkably, in that single attempt, the sample possessed a diastereomeric ratio of 82:18 [80].



4. Reactions of sulfenate anions

The synthetic utility of sulfenate anions will ultimately be defined by the breadth of their chemistry and by new discoveries building off their potential for stereochemical syntheses. Recent work has provided information on both of these fronts.

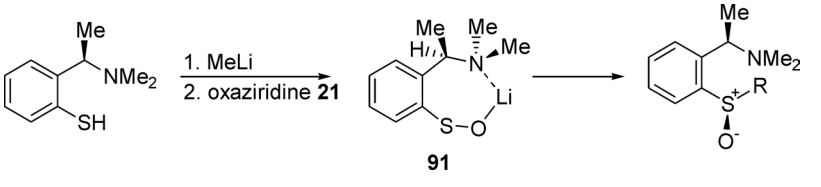
4.1 *O- vs. S-alkylation*

The ratio of sulfenic acid esters and sulfoxides, arising from *O*- and *S*-alkylation respectively, depends largely on the reaction conditions. Parameters such as polarity of solvent, phase-transfer reagents, reaction temperature and the nature of the alkylating agent are all important.

Methyl iodide and benzyl bromide tend to favour *S*-attack [32, 48]. Agents such as methyl fluorosulfate and dimethyl sulfate [81] favour formation of the sulfenate ester, as do polar solvents such as DMF [48] or the addition of crown ethers [82]. The reagent dependence has been attributed to hard electrophiles preferring to react with oxygen in a loose transition state possessing S_N1 character, while soft electrophiles are involved in an S_N2 type reaction with the sulfur [81]. Hard and soft silylating agents are believed to follow the same trends [23]. Polar solvents and crown ethers are thought to sequester sulfenate counterions, creating a naked sulfenate oxygen available for alkylation [82].

4.2 *Asymmetric induction*

Because sulfenate anions contain a divalent sulfur possessing a plane of symmetry, they lack chirality. However, sulfenates are prochiral, since alkylation at sulfur creates a stereogenic sulfur if that sulfur's substituents differ. To achieve an enriched sulfinyl group, one must differentiate between the two pairs of electrons that reside on the sulfur atom. The Perrio group suggested that selectivity for one pair of electrons of the sulfenate could be realized if the sulfenate contained a stereogenic centre. Moreover, if steric barriers could be implemented and restricted conformations imposed, diastereoselection of the sulfur lone pairs could be possible as alkylation proceeds [83]. As demonstrated in scheme 29, through chelation of the nitrogen with the lithium counterion (**91**), the methyl group at the stereogenic centre hinders alkylation from the upper face and therefore forces alkylation from the bottom.

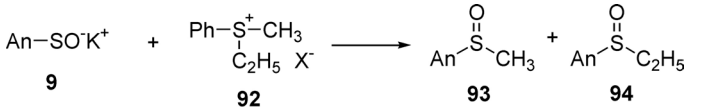


91

SCHEME 29

Preferential alkylation from the bottom face led to good selectivities for methyl- (dr 84:16), ethyl- (dr 84:16), and allylation (dr 81:19). Benzylation occurred with the greatest selectivity, offering a dr of 98:2! A remarkable and synthetically useful feature of this approach is that it affords sulfoxides with an opposite configuration at sulfur than the well-documented diastereoselective oxidation of sulfides [84], thus offering complementary methodologies to chiral sulfoxides.

Kobayashi observed a transfer of chirality in the alkylation of sulfenate anions with optically active sulfonium salts [82]. Reaction of (*S*)-(+)-methylethylphenylsulfonium d-camphorsulfonate (**92**) with anthraquinone-1-sulfenate (**9**) in acetonitrile for 4 days affords a mixture of optically active sulfoxides **93** and **94** in yields of 10.4% and 43.7%, respectively (scheme 30). The reaction time was reduced to one day upon the addition of 18-crown-6 to the reaction mixture (table 13). The maximum stereoinduction that could be achieved with this protocol was an ee of 23.8%.



9 **92** **93** **94**

An = 1-anthraquinoyl; X^- = d-camphorsulfonate

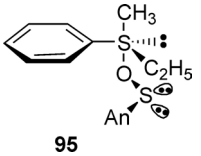
SCHEME 30

Table 13. Alkylation of sulfenate anions with optically active sulfonium salts.

Sulfonium salt	Yield (%) **93**	**94**	ee of **94**
(*S*)-(+)-**92**	10.4	43.7	23.8(*S*)
(*S*)-(+)-**92**[a]	7.5	28.5	20.5(*S*)
(*R*)-(−)-**92**	5.3	22.0	19.9 (*R*)

[a]0.2 equiv. of 18-crown-6 added to the mixture.

Since preliminary experiments indicated that sulfonium salts do not follow the typical sulfenate alkylation observations outlined in section 4.1, an alternative mechanism was proposed. Asymmetric induction is thought to occur *via* formation of *O*-sulfurane intermediate **95**. A donor–acceptor stabilization becomes possible between the phenyl group and the anthraquinoyl group if the phenyl group adopts the equatorial position. Attack is thus directed at the bottom face and gives preferential formation of the *S*-ethyl sulfoxide (**94**) due to the lone pair on sulfur that is not sterically hindered by the ethyl group. Notwithstanding the achievements in chirality, an important issue arises from this work: the simple vision of substitution *via S* or *O* cannot be employed to account for all observations. The researcher should be wary of other possibilities, particularly with electrophiles capable of higher coordination.



95

4.3 *Chemical properties of arenesulfenate anions*

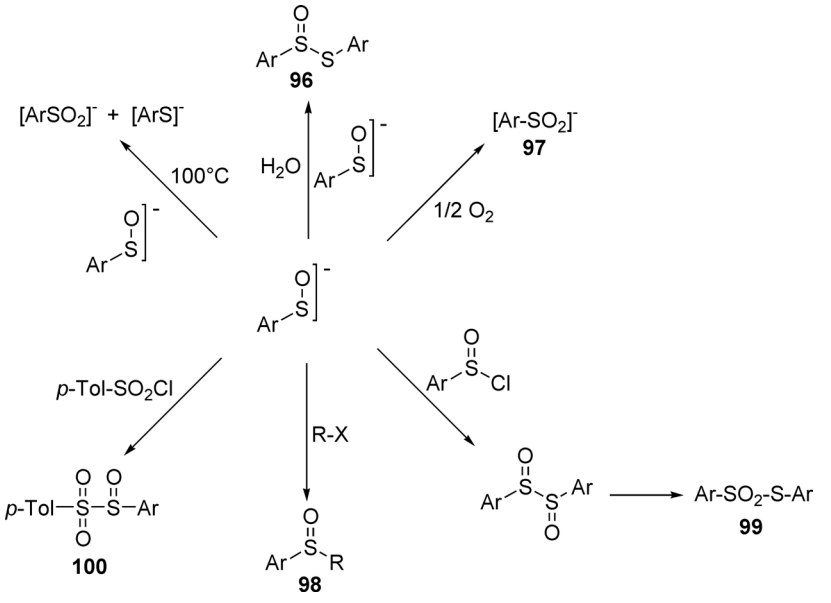
When thiosulfinates are reacted with organometallic reagents sulfenic acid salts are produced. The 1973 review by Vinkler and Klivényi outlines the chemical properties of arenesulfenic acid salts liberated by organometallic reagents [16]. It was shown that sulfenate anions (i) react in water to afford thiosulfinates (**96**); (ii) can autoxidize to sulfinic acid salts (**97**) by standing in air; (iii) are prone to disproportionation on heating; (iv) react with alkyl halides to give sulfoxides (**98**); (v) react with arylsulfinyl chlorides to give thiosulfonates (**99**) after rearrangement; and (vi) react with *p*-toluenesulfonyl chloride to afford sulfinyl sulfones (**100**) (scheme 31). The chemical summary outlined in this early review clearly indicates the reactive nature of the sulfenate in addition to its disdain for atmospheric conditions and elevated temperatures [16].

4.4 *Preparation of sulfoxides*

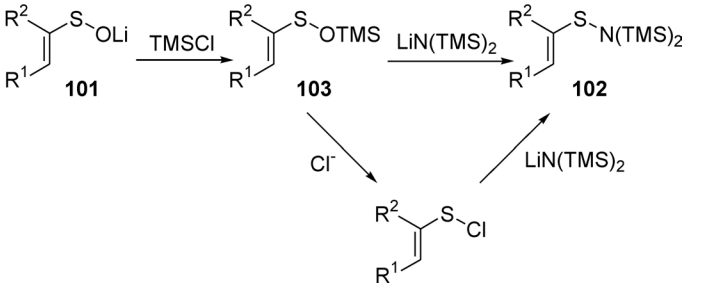
Not surprisingly, sulfenate anions have long served as precursors to sulfoxides. Such a facile reaction, forming a stable product is an easy means of establishing the structure of the sulfenate. Examples of sulfoxide formation have been addressed in section 3.

4.5 *Preparation of sulfenamides and sulfonamides*

Schwan suggested that, since 1-alkenesulfenates (**101**) exist in solution for a period of time with hexamethyldisilazane, it might be conceivable that sulfenates **101** be converted into the corresponding 1-alkenesulfenamides (**102**) by modifying their normally nucleophilic sulfur to an electrophilic one (scheme 32) [55].



SCHEME 31

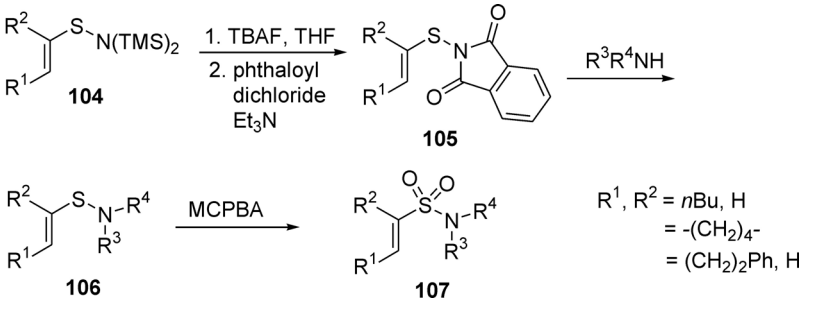


SCHEME 32

A small family of TMS-X reagents were tested for compatibility with the reaction [23]. Although TMSI gave the highest yield of sulfenamide, a disulfide by-product was observed. Conversely, TMSCl gave a slightly lower yield of sulfenamide, but no side-products were observed. Given this result, the reaction was optimized to involve 2 equiv. of LiHMDS when generating the sulfenate. Mechanistically the reaction pathway is unclear since trimethylsilyl sulfenate **103** should show reactivity towards both the lithium amide and the chloride ion. Despite the unknown pathway, isolation of sulfenamides **102** confirms a change of philicity at sulfur.

Attempts were made to adapt sulfenamides of the structure **104** to serve as a general source of α,β-unsaturated sulfenamides. Species **104** could not directly be converted into other sulfenamides, but it was possible to effect a one-pot conversion of compounds **104** into *N*-(1-alkenylthio)phthalimides **105**. Following the lead of Harpp and Back [85], transamination reactions on compounds **105** were used to produce a library of 1-alkenesulfenamides bearing different alkyl groups on nitrogen (**106**) [56]. To ensure complete characterization the alkenesulfenamides were oxidized to their corresponding alkenesulfonamides (**107**) [56], demonstrating a synthetic protocol for α, β-unsaturated sulfonamides (scheme 33). Other preparative methods for unsaturated sulfonamides have been developed [86–89] as these compounds are becoming increasingly important as drug candidates. They have been recognized for their value

as inhibitors of cysteine proteases [90], as endothelin-A receptor antagonists [91, 92] and have been incorporated into molecules to serve as peptide isosteres [86, 93].



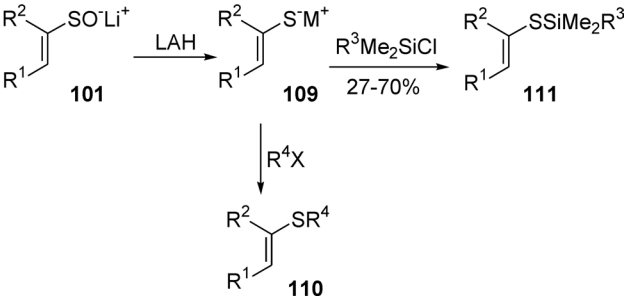
SCHEME 33

N-Silylated sulfenamides **104** were also shown to undergo desilylation in the presence of carbonyl compounds that do not bear α-hydrogens, yielding 1-alkenesulfenimines (**108**, scheme 34). A few α,β-unsaturated sulfenamides possessing no groups on the nitrogen could also be made, but showed limited stability [55].

SCHEME 34

4.6 *Preparation of thiol derivatives*

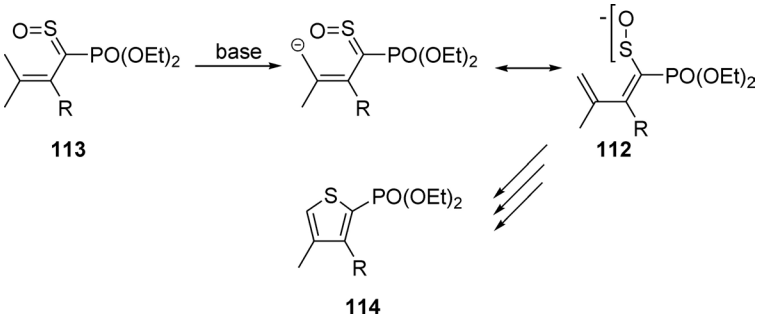
Thiols can be prepared from sulfenates by the method outlined by Fokin [77] as outlined in section 3.3.3. α,β-Unsaturated thiolates (**109**) can be prepared by LAH reduction of 1-alkenesulfenates (**101**), a process that maintains the double bond geometry if performed at −78 °C. Simple alkyl quenching of the thiolate below −40 °C leads to *E*-1-alkenylsulfides (**110**), while silylation with a R^3Me_2X reagents gives *E*-1-alkenylthiosilanes (**111**), which can act as protected enethiols along a synthetic pathway (scheme 35) [57]. The configuration of the double bond survives the reduction conditions and thiolate alkylation as long as a low temperature is maintained.



SCHEME 35

4.7 *Preparation of thiophenes*

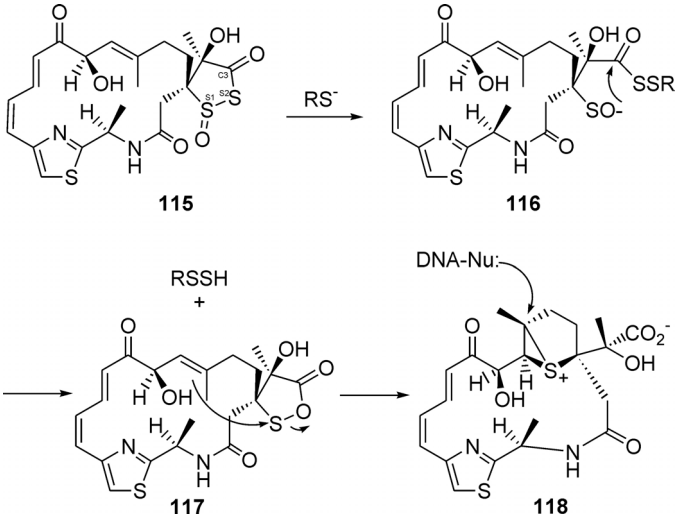
Thiophene-2-phosphonates have been prepared by way of a sequence commencing with deprotonation of α,β-unsaturated sulfines [94]. In chemistry based on that presented in section 3.2.3, sulfenate **112** was generated from deprotonation of sulfine **113**. Internal cyclization of sulfenate **112** followed by further reactions incorporating another molecule of SO_2 and Pummerer-like chemistry leads to thiophene **114** (scheme 36).



SCHEME 36

5. Biological importance

Sulfenate anions are slowly garnering recognition as possible intermediates in biologically important mechanisms [26, 95–106]. Several groups are suggesting that a sulfenate rather than, or in accompaniment with, a sulfenic acid is an intermediate in the oxidation of cysteinyl residues of proteins. For example, strong evidence exists that the Cys-SO^- form of αCys114-SOH is involved in the active site coordination chemistry of nitrile hydratase from *Rhodococcus N-771*, a bacterial enzyme that catalyzes the hydration of nitrile to carboxamides [26].



SCHEME 37

5.1 *Activation of leinamycin – DNA alkylation*

Leinamycin is a natural product that displays potent anticancer activity, and has been shown by Gates to be activated by thiols and to act as a DNA-damaging agent [102]. Herein lies

the most compelling evidence for a sulfenate as a biological intermediate. The DNA damage results from attack of thiols on the 1,2-dithiolan-3-one 1-oxide heterocycle (**115**), which produces sulfenate intermediate **116**. Sulfenate **116** undergoes an intramolecular carbonyl attack generating a cyclic mixed sulfenic/carboxylic anhydride (**117**). Heterocycle **117** is prone to intramolecular attack to afford episulfonium ion **118**, which is offered as the DNA damaging agent (scheme 37) [100, 101].

A simple analogue of the 1,2-dithiolan-3-one 1-oxide heterocycle of leinamycin was used as a model for theoretical studies at the B3LYP/6-31G* level to examine the attack of methyl thiolate on each of the three electrophilic centres (S1, S2, C3). Favoured by 6 kcal mol^{-1} with a barrier of activation of only 19.2 kcal mol^{-1}, attack of thiolate at S2 leading to the formation of sulfenate **116** was shown to be an energetically reasonable mechanism [101].

6. Summary and conclusions

In an area of organosulfur chemistry that remains relatively unexplored resides a potent nucleophile capable of numerous transformations. An increasing number of methods are available for the preparation of sulfenate anions, including metal insertion, addition–elimination reactions, ring openings, rearrangements and oxidations.

Within the last two years there have been two reports of diastereoselective alkylation of sulfenates. These two examples portend further discoveries and the development of an area complementary to the diastereoselective oxidation of sulfides. Through basic manipulation of the sulfenates, one can obtain sulfenamides, sulfonamides and thiol derivatives.

Finally, the burgeoning chemistry of organometallic *S*-sulfenato or *O*-sulfenato complexes has led to several useful contributions [103, 106–112]. This area of research is outside the scope of the current review since organic sulfenates have not yet been employed for the preparation of the inorganic sulfenato *S*-complexes. Perhaps the research summarized herein can serve as a springboard for new organic sulfenate chemistry in organometallic synthesis.

Overall, the appreciation of the sulfenate anion as a reactive intermediate in biological chemistry and as a valuable tool in synthesis is now being realized. Continued research in the area should lead to the development of the sulfenic acid anion as a valuable sulfur nucleophile.

Acknowledgments

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