The sulfonamide motif as a synthetic tool

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Jonathan Wilden obtained his PhD from the University of Southampton in 2001 having worked on the total synthesis of the marine natural product pseudopterosin with Professor David Harrowven. He then moved to the University of Sussex, Brighton, UK where his interest in sulfonamide chemistry began, working with Professor Steve Caddick. In 2004 he was appointed lecturer at University College London where his research interests include the synthesis of medicinally important compounds and exploitation of the sulfonamide group in organic synthesis.

Sulfonamides are well known motifs in medicinal chemistry, forming a large family of antibacterial agents as well as being found in numerous other drugs. The chemistry of this functional group, however, is less well documented. This review seeks to bring together the various applications and advantages of this motif in organic synthesis, which includes the sulfonamide as an activating group, protecting group, leaving group and as a molecular scaffold.

Keywords: sulfonamides, medicinal chemistry, reactivity, organic synthesis

1. Introduction

The sulfonamide group is a tool well known to the medicinal chemist. Since the introduction in the 1930s of the so-called 'sulfa-drugs' such as sulfanilamide and Prontosil (shown in Fig. 1), sulfonamide-containing compounds have found widespread use in the pharmaceutical industry and the motif still considered valuable and safe for drug development.[1]

These compounds elicit their biological effect by competing with the structurally-related compound *p*-aminobenzoic acid (Fig. 1) which is involved in the synthesis of folate in bacterial cells. Since mammals do not synthesise folate but instead acquire it from the diet, a critical bacterial pathway can be inhibited without affecting the patient to which the drug has been administered. This strategy of replacing carboxylic acid and amide groups with sulfonamides has been used extensively in medicinal chemistry. The properties of the sulfonamide motif (particularly aryl and heteroaryl sulfonamides) of being resistant to hydrolysis while being transition-state mimetics of the peptide bond has endeared them to the medicinal chemist over the years. Some more recent examples include the blockbuster drugs Viagra and Celebrex shown in Fig. 2.

There is, however,, much more to this functional group than just its medicinal value. An examination of the literature over the last fifty years reveals a fascinating reactivity profile for a group, which has possibly been under exploited by the synthetic chemist. In synthesis, the sulfonamide has been extensively used as a protecting group for amines and as a convenient halophilic oxidising/halogenating agent in the forms of chloramine-B **1** and chloramine-T **2**.[2]

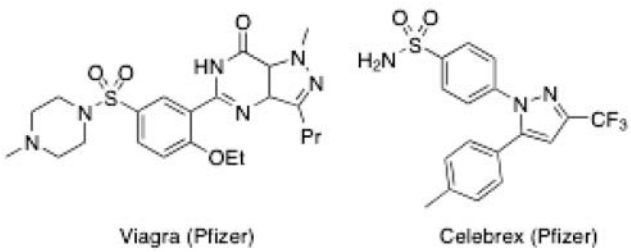

Fig. 2

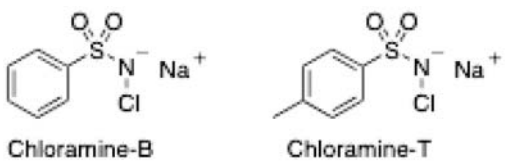

Fig. 3

The deployment of a sulfonamide with its unique properties to effect a particular synthetic transformation is, however, relatively rare in the chemical literature. This short review seeks to re-examine some of the reactions of sulfonamides and highlight the ways in which the properties and reactivity of this motif can be exploited by the synthetic as well as the medicinal chemist. The reactions of similar compounds such as sulfones, sulfonate esters and sulfoxides have been extensively explored

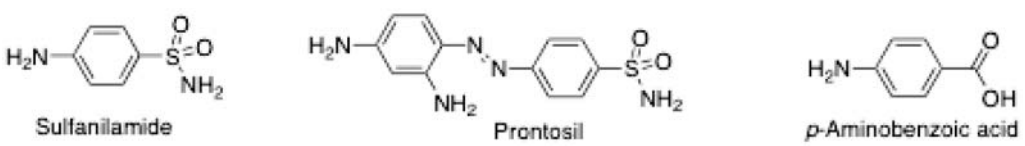

Fig. 1

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and as such will not be covered here. Similarly, the synthesis of sulfonamide compounds will not be covered by this review since this is more than adequately described elsewhere; two recent examples are given in references 3 and 4.

2. Properties of sulfonamides

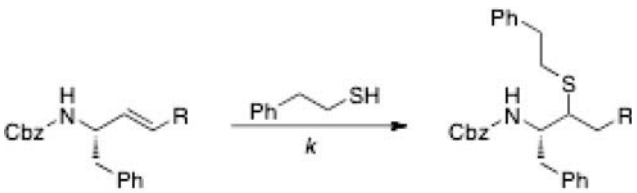
It is often assumed that the sulfonamide motif behaves in a similar manner to carbonyl compounds such as esters and amides and related sulfur compounds such as sulfones, sulfoxides and sulfonate esters. While there is some truth in this assumption, there are many more interesting differences in their reactivity, which are highlighted below and form the basis for much of the synthetic utility of this group.

2.1 Electron withdrawing capacity

Carbonyl compounds, sulfones, sulfonate esters and sulfonamides all exert an electron-withdrawing effect on surrounding atoms both mesomerically and inductively. The effect of the sulfonamide is, however, the least electron-withdrawing component of all of these groups. This is even more surprising when faced with the fact that sulfonate esters, seemingly very similar compounds are the most electron withdrawing. This effect has been elegantly demonstrated by Roush *et al*.[5] who have shown that the rate of 1,4-addition of a simple thiol nucleophile to an alkene bearing a sulfonate ester is *ca* 3000 times faster than that to one bearing the corresponding sulfonamide, with the comparable carbonyl compounds being significantly faster than the sulfonamide but slower than the sulfonate ester (Scheme 1, Table 1).

2.2 As a leaving group

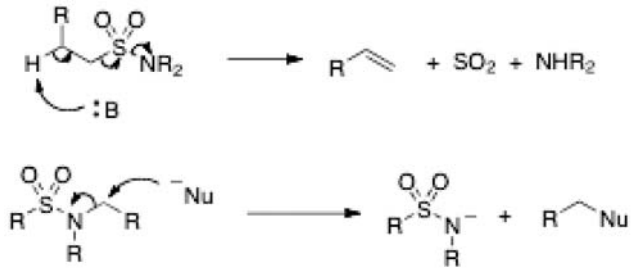
Sulfonamides (in common with sulfones and sulfonate esters) can also act as a leaving group under certain circumstanses, often with the elimination of SO_2 (Scheme 2). These reactions will be covered in detail in later sections.



Scheme 1

Table 1

R	Relative Rate, *k*
SO_3Ph	3000
COMe	2700
$SO_2N(Me)OBn$	150
SO_2Ph	120
SO_3Et	90
SO_2NHOBn	50
CO_2Me	17
$SO_2N(Me)Bn$	3
SO_2NHBn	1



Scheme 2

2.3 Resistance to nucleophilic α-substitution

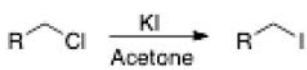
One of the most striking differences between carbonyl compounds and sulfonyl compounds is the resistance of the latter to nucleophilic displacement of leaving groups at the site α- to the sulfonyl unit. The sulfonyl group deactivates this site whereas the carbonyl group, and other electron withdrawing groups such as nitriles, activate it. The effect is easily demonstrated by comparing the reaction of α-chlorosulfonyl compounds and α-chlorocarbonyl compounds with potassium iodide in acetone. Scheme 3 illustrates that the sulfonyl compounds are essentially unreactive whereas the carbonyl compounds readily are readily substituted.

Both the activating effect of the carbonyl group and the deactivating effect of the sulfonyl group have been demonstrated by Bordwell *et al*. in the 1950s and 1960s.[6] In an elegant demonstration of their reactivity, Bordwell's group demonstrated that the depression in reactivity of compounds such as the α-chlorosulfonyl compound above was uniquely attributable to the steric effects of the sulfonyl group, since it was observed that the related compound, (when R = *p*-Tol-SO_2CH=CH) where the mesomeric effect of the sulfonyl group would still be expected but the steric effect is largely eliminated, reacts with nucleophiles around 14 times faster than allyl chloride (Table 2).

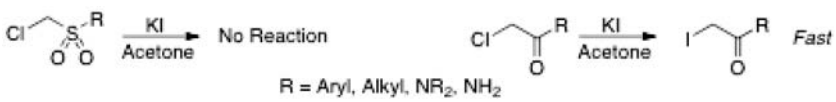
Other sulfonyl compounds and nucleophiles were also examined. Most notably for this review, the reaction of α-chloromethanesulfonamides with amines and phenoxides was studied and these compounds were found to react similarly to other sulfonyl compounds. Indeed, it was noted that the reaction of phenoxide with chloromethanesulfonanilide **3** failed to yield any displacement product, and the chloromethanesulfonamide **4**, after treatment with aniline for 14 days, had released only 23% of its halogen (Scheme 4).[7]

The origin of this deactivating effect has been attributed to the steric and polar effects as described by Ingold. The approach

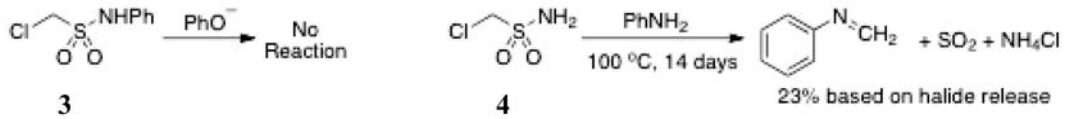
Table 2



R	Relative Rate, *k*
$CH_3(CH_2)_2$	1
p-Tol-SO_2	<0.02
CH_2=CH	80
p-Tol-SO_2CH=CH	1100
N≡C–CH=CH	1400
N≡C	3000



Scheme 3



Scheme 4

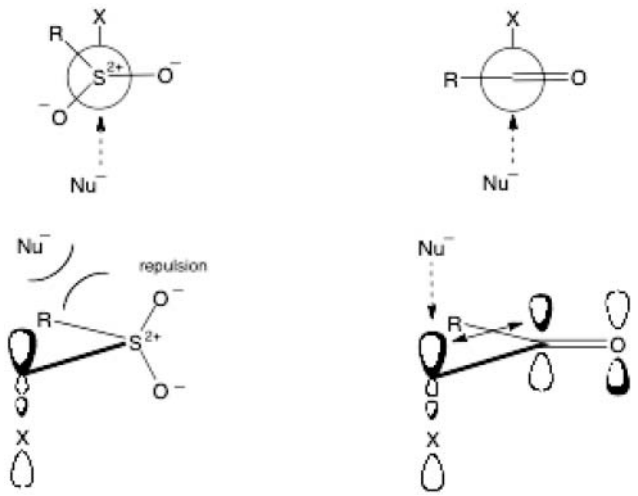


Fig. 4

of a nucleophile to the α-halosulfonamide is hindered by an atom of high electron density. This is in sharp contrast to the comparable approach to an α-halo carbonyl compound where the approach is essentially unhindered and quite possibly actively assisted by interaction with the vacant π*-orbital located on the carbonyl carbon atom, which lowers the energy of the vacant σ*-orbital of the C-X bond and facilitates nucleophilic attack (Fig. 4).

2.4 C–H and N–H Acidity

In common with carbonyl compounds the sulfonamide group stabilises the α-carbanion although less so than the corresponding carbonyl group (pKa *ca* 30 for a sulfonamide α-CH and 25 for an amide CH). For the deprotonated species, the electron density for an enolate resides predominantly on the oxygen atom, whereas for a deprotonated sulfonamide it has been shown both experimentally and by computational methods that the metal and most of the electron density is associated with the α-carbon atom as shown in Scheme 5.[8]

Conversely the N–H acidity is significantly higher for sulfonamides than it is for amides (pKa 25 for an amide NH compared to *ca* 8 for a sulfonamide NH). This leads to the unusual dichotomy in which the sulfonamide group stabilises the α-carbanion less than the corresponding amide, whereas the nitrogen-centred anion is stabilised more by the sulfonamide than the comparable amide.

3. Reactions of sulfonamides

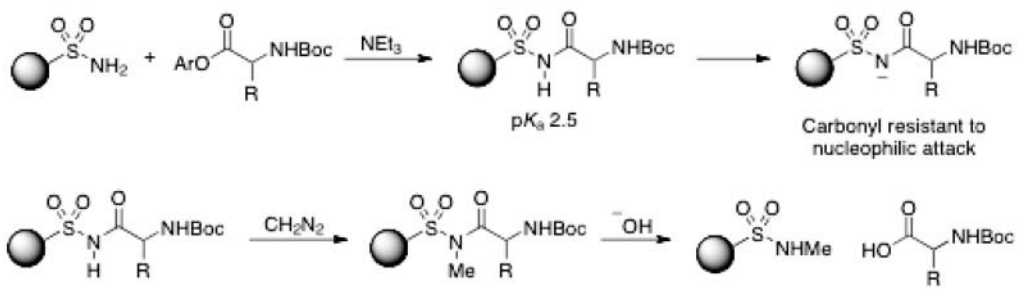
Categorisation of the reactions of sulfonamides where they have been exploited as synthetic tools is extremely difficult as they often display multiple features in any one process. For example, a single process can involve the sulfonamide behaving as a radical carrier, leaving group, protecting group and/or activating group at various stages of the particular process. The following sections will therefore adopt a broadly chronological approach to the applications of these compounds and will highlight the versatility this group has displayed in organic reactions over the years.

3.1 Early reactions: 1960s and 1970s

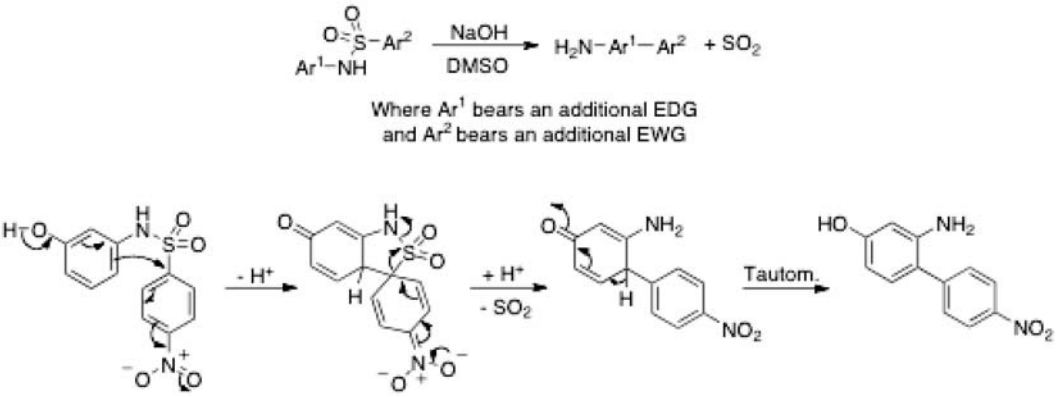
The application of sulfonamides since the 1940s has been mainly medicinal in nature focusing on their application in the treatment of bacterial infection. In the 1960s and 1970s however, this group began to be exploited for synthetic purposes as well as medicinal ones.

One of the first applications of the sulfonamide in synthesis was documented in 1971 by Kenner *et al.*[9, 10] who described the use of a sulfonamide as a 'safety catch' linker for solid phase peptide synthesis. They reported that amino acid active esters could be coupled with solid-supported primary sulfonamides and were suitable scaffolds for peptide synthesis under basic coupling conditions since the pKa of the sulfonamide was sufficiently low to be deprotonated under even mildly basic conditions and to render the acyl unit resistant to attack by nucleophiles. Cleavage from the resin could be achieved by alkylation of the sulfonamide NH with diazomethane followed by treatment with base to liberate the free peptide (Scheme 6).

Scheme 5



Scheme 6



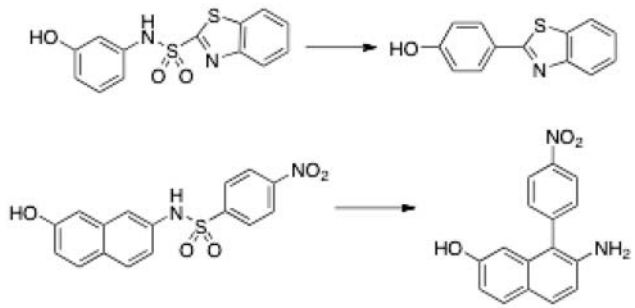
Scheme 7

Remarkably, this early disclosure received little attention at the time and was largely ignored throughout the development of solid phase chemistry throughout the 1980s and early 1990s. Problems such as poor loading efficiencies and low reactivity compared to other solid phase methods in addition to the necessity to employ diazomethane to cleave the peptide were importatnt. It was not until the mid 1990s that the utility of this approach to solid phase synthesis was finally recognised (*vide infra*).

An early solution phase exploitation of sulfonamide chemistry was disclosed just a year later in 1972 by Waldau and Pütter who described the synthesis of biaryls, stilbenes, benzo[*c*]cinnolines and dibenz[*c,mn*] acridines from sulfonamides (in a short communication that, interestingly, cites no references).[11] Their paper outlines the rearrangement of an electron rich aryl ring linked to an electron deficient aryl group by a sulfonamide. Heating these compounds with base in dimethylsulfoxide led to the biaryl products in moderate to good yields. The general scheme and a mechanism are given in Scheme 7:

The reaction is successful for a variety of aromatic systems providing that: (i) at least one site *ortho* to the nitrogen atom is unsubstituted; (ii) the hydroxy group in the same ring (Ar^1) is appropriately positioned to direct nucleophilic attack on the second (Ar^2), electron-deficient ring; and (iii) there is an electron-withdrawing group suitably positioned in Ar^2. Of particular note is the ability to synthesise hetero-biaryls (where the heteroaromatic is the electron deficient ring) and the application of naphthalene rings to the reaction (Scheme 8).

In all of these examples, the function of the sulfonamide is two-fold. Its primary function is to act as a cleavable linker between the two aromatic groups ultimately behaving as a leaving group. The electron-withdrawing capacity of the group also serves to activate further the electron deficient ring towards nucleophilic attack.



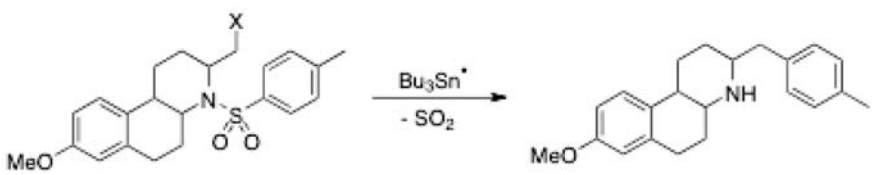
Scheme 8

Despite the clear limitations in the scope of the substrates, requiring one electron rich component and one electron deficient component, this method was an ingenious way of synthesising compounds that even today with the modern tools of transition metal cross-coupling reactions would still be considered challenging.

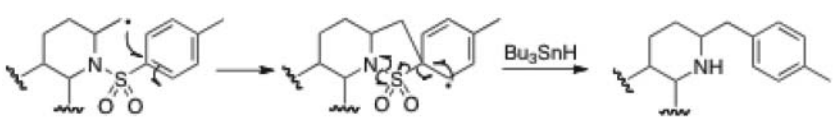
The ability of the sulfonyl unit to behave as a radical leaving group was first noted in the early 1970s by the work of Lovan and Speckamp who, while pursuing a synthesis of functionalised heterocycles, discovered that the aryl group from the sulfonamide under free radical conditions could migrate to a pendant alkyl group with loss of SO_2 (Scheme 9).[12]

The mechanism (Scheme 10) was shown to be an *ipso*-attack of the primary radical onto the aromatic ring bearing the sulfonamide followed by elimination of SO_2.

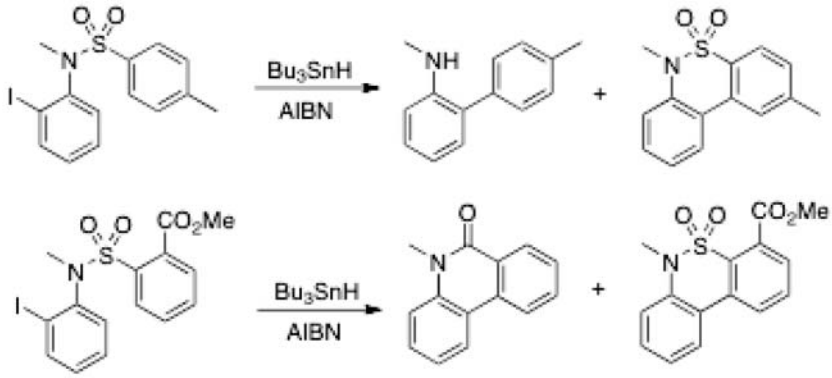
Much work flowed from the group of Speckamp in exploring the application and scope of these reactions. The same



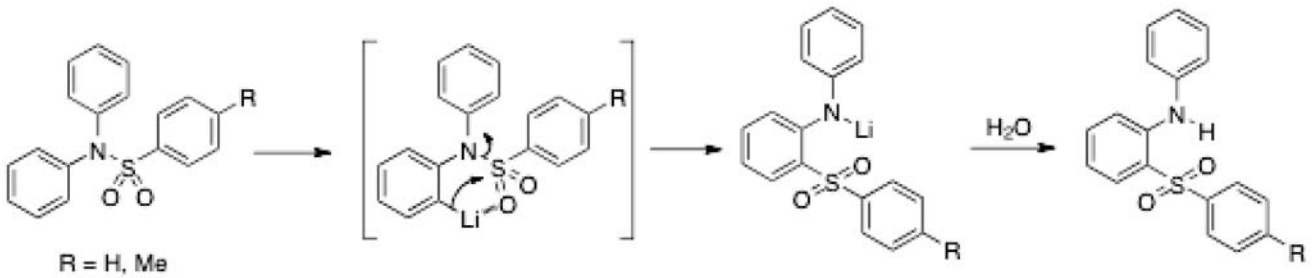
Scheme 9



Scheme 10



Scheme 11



Scheme 12

strategy, outlined in Scheme 11, was later exploited by Pennell and Motherwell in 1991 in the preparation of biaryl systems such as **5** and in the synthesis of tricyclic systems such as **6**.[13] As was observed by Speckamp's work throughout the 1970s, the competing reaction of direct addition of the radical to the aryl group was also obtained in varying amounts.

This work was also followed by a similar approach to arylethanols and arylethylamines by Tada's group in 2003.[14]

Continuing a body of work in the early 1970s, it was noticed by Hellwinkel and Supp that treatment of *N*-aryl aromatic sulfonamides with alkyllithium reagents led to *ortho*-lithiation followed by an unusual rearrangement in which the diaryl sulfone was formed (Scheme 12).[15]

This reaction proved to be a method of preparing non-symmetrical aryl sulfones, but has received little synthetic attention. The original paper does however make the statement 'Remarkably, the phenyl ring bound to the nitrogen is clearly the one which is metalated' and suggests the importance of the contribution of the resonance structure **7**, shown in Fig. 5, as an explanation for their observations.

Given the importance sulfonamides have found in the directed *ortho*-metallation of aromatic compounds, Supp should be considered one of the pioneers of this work by virtue of these observations.

Fig. 5

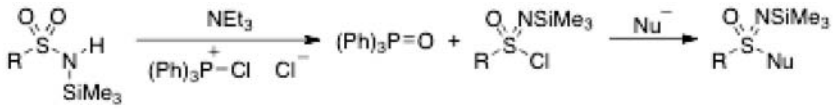
3.2 Work in the 1980s and 1990s

In terms of synthetic utility, little in the way of new sulfonamide chemistry emerged in the 1980s. Sulfonamides continued to be useful protecting groups but little was described with respect to their own chemistry. In 1993 however, Roy described a method of the conversion of the sulfonamide moiety into the rather more unusual sulfonimidoyl halides and sulfonimidates.[16] This conversion is of note for being one of the few examples of the sulfonamide as an intermediate in a synthetic route and due to the utility of the sulfonimidates in materials and polymer chemistry. Roy's route involved an *N*-silylated sulfonamide reacting with chlorotriphenylphosphonium chloride to generate the sulfonimidoyl chloride which then can be isolated or react with a nucleophile to form the sulfonimidate (Scheme 13).

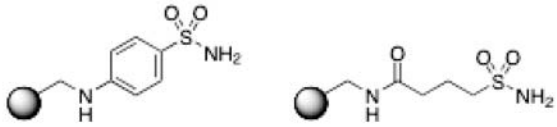
The 1990s saw a boom in the application of solid phase synthesis in organic chemistry and the original approach by Kenner and coworkers in 1971 (*vide supra*) was finally exploited to its full potential. The modified linkers **8** and **9** were introduced by the group of Ellman in order to address some of the initial problems of Kenner's sulfamoylated resin as well as the introduction of iodoacetonitrile as the alkylating agent in the place of diazomethane (Scheme 14).[17] This method has found particular application in the preparation of peptide thioesters in the emerging field of peptide ligation.

3.3 2000s to present

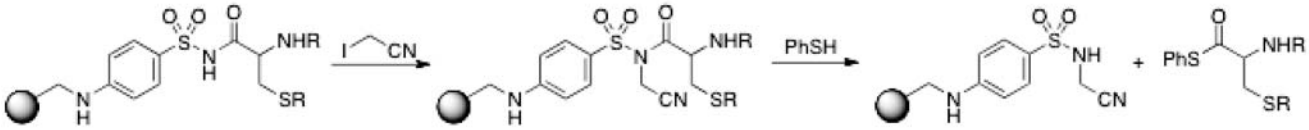
A large number of papers exploiting the innate reactivity and properties of the sulfonamide were published in this decade. Many have built on the early chemistry described above, however new chemistry and applications continued to be



Scheme 13

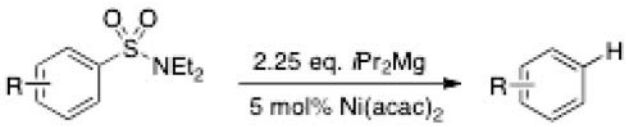


Modified versions of Kenner's safety-catch linker



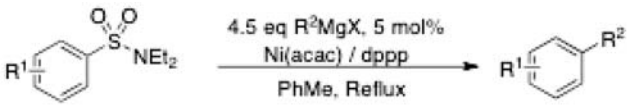
Activation of sulfamoyl resin by acetonitrile and cleavage to give a peptide thioester

Scheme 14



R = EWG, EDG, SiR_3, Alkyl, Aryl

Scheme 15



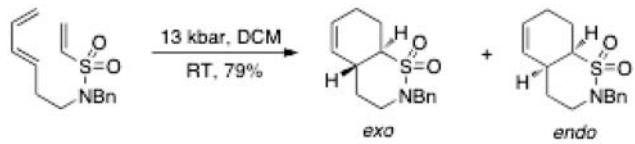
Scheme 16

developed. In 2004, Milburn and Snieckus added a new application to the portfolio of sulfonamide chemistry. The work of Snieckus' group demonstrated that it was possible for tertiary aryl sulfonamides to undergo Ni(0)-catalysed reductive cleavage with β-hydride donors such as *i*PrMgCl and *i*Pr_2Mg under mild conditions and in good yields (Scheme 15)[18]

Snieckus also outlined an exciting extension to this work: an unprecedented cross-coupling protocol for aryl sulfonamides (Scheme 16).

These reactions have great synthetic potential, and remove the usual requirement for a halide to be attached to the ring. The sulfonamide, being electron withdrawing, also alters the reactivity in terms of the directing effect towards electrophilic aromatic substitution and therefore allows for functionalisation of the ring that would not be possible with a halide or triflate.

The use of the sulfonamide group as a scaffold in solid phase chemistry is now a routine and advantageous strategy in that area. In general solution-phase organic synthesis, however,, the strategy of utilising the sulfonamide as a tethering scaffold has received less attention, due partly to the perceived difficulties in removing the sulfonyl unit at the end of the reaction. This has been addressed, however, in a number of papers



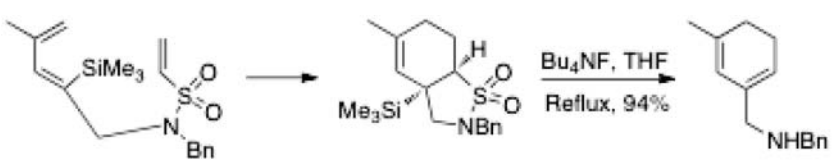
Scheme 17

published by the group of Metz throughout the last decade. In their studies of intramolecular Diels–Alder cycloadditions, the group has shown that the sulfonamide group can be exploited as a tether and an electron-withdrawing activating group in the following intramolecular cycloaddition (Scheme 17).[19] It was also noted that both yield and *endo*-selectivity could be improved by employing high pressures (12–13 kbar) at low temperatures (RT or below) compared to their previous results obtained in refluxing toluene.

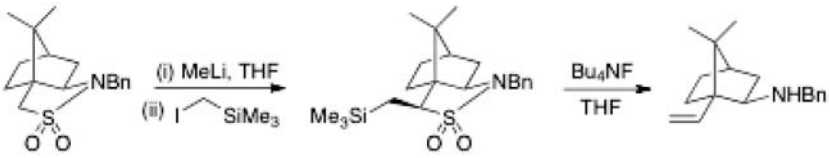
Metz followed up this strategy to include dienes such as furans which in an intermolecular fashion are often unreactive towards most dienophiles except the most activated examples.[20] Their work has shown that the sulfonamide moiety can be removed from the cyclised products by reduction with Raney nickel. However, it is their paper from early 2008 that highlights the utility of the chemistry of the sulfonamide motif. In work directed towards new methods of removing the sulfonamide tether, Metz showed that the latent leaving-group capacity of the sulfonamide could be induced by introducing a silicon group into the molecule in a position that following the cycloaddition would eliminate SO_2 on treatment with fluoride ion (Scheme 18).[21]

Alkylation of other γ- and δ-sultams with iodotrimethylsilane followed by treatment with fluoride led to the desulfurised products with simultaneous methylenation in a reaction sequence that once again showcases the anion-stabilising capabilities of the sulfonamide and its ability to act as a leaving group under specific reaction conditions (Scheme 19).

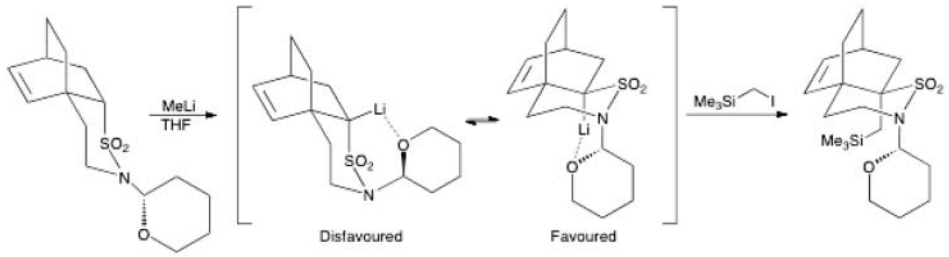
Furthermore, the authors also note that C-deprotonation of the sulfonamides of the type **10** could be facilitated by the attachment of a tetrahydropyranyl (THP) moiety to the sulfonamide nitrogen atom which stabilises the α-anion via a



Scheme 18



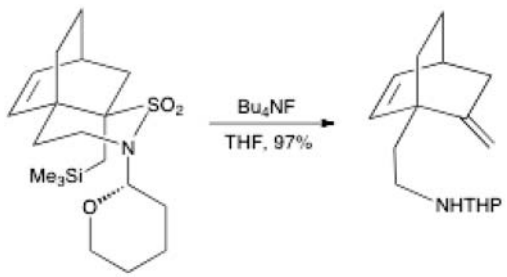
Scheme 19



Scheme 20

chelation effect and highlights the propensity of alkyl sulfonamides in their metallated form to bear the metal and electron density on the carbon atom rather than the sulfonamide oxygen atom demonstrating their different reactivity compared to carbonyl compounds (Scheme 20).[21]

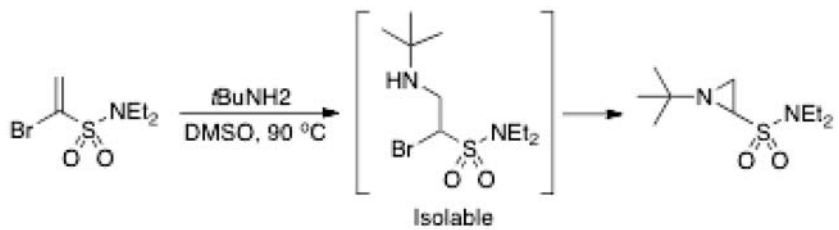
The major product arises from the known equilibrium between metalated sulfonyl compounds which leads to the *endo*-methylene silane. Exposure of this compound to Bu_4NF in THF then leads to the desulfonylated product in good yield (Scheme 21).



Scheme 21

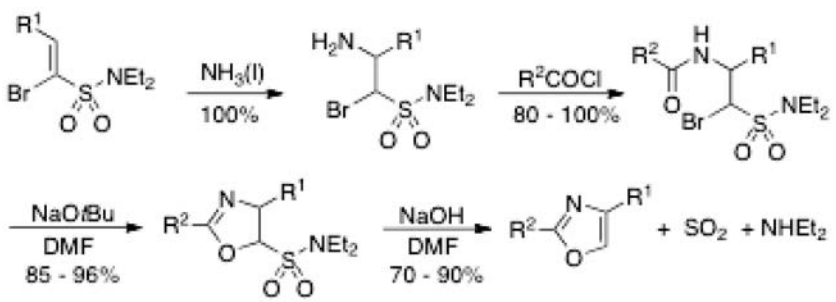
Our own group has been interested in the chemistry of sulfonamides for some time and has focused specifically on utilising its chemistry as a tool in synthesis. We were first struck by the observation of Vessiere and coworkers[22] that compounds such as **11** could undergo the unusual displacement process at the α-position of a sulfonamide by virtue of the process being intramolecular (Scheme 22).

This dichotomy of the displacement being feasible while intramolecular but virtually impossible when an intermolecular process had received little attention in the literature. Our work exploited the mild electron-withdrawing capacity of the vinyl sulfonamide, the resistance to undergo competing intermolecular addition and the 'allowed' intramolecular displacement reaction of these compounds and the leaving group propensity of the sulfonyl unit to develop a mild, regioselective synthesis of oxazoles (Scheme 23).[23]



11

Scheme 22



Scheme 23

4. Concluding remarks

This short review charts the development of the sulfonamide as a synthetic handle over the last 40 years. During this time there has been a slow development of the chemistry that has bought us to the present day where this group is no longer simply seen as highly stable protecting group or a blocking group for amines. Sulfonamides have an interesting portfolio of properties and reactions, which, when appropriately deployed, can offer real advantages in the synthesis of complex organic molecules. Further research will undoubtedly reveal new and useful applications which may make this motif as useful to the organic chemist as it currently is to the medicinal chemist.

Received 7 July 2010; accepted 1 September 2010
Paper 1000292 *doi: 10.3184/030823410X12857514635822*
Published online: 22 October 2010

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