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RESEARCH ARTICLE

The synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides from 1,2-thiazine 1-oxides

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This paper presents a new approach to the synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides, sulfonamide analogues of the 'privileged' 1,4-benzodiazepine pharmacophore. The key steps during this synthesis are the hetero Diels-Alder reaction of an *N*-sulfinylamine dienophile with a diene to give a 1,2-thiazine 1-oxide which is then converted into a *N*-(*o*-azidobenzenesulfonyl)-1,2-amino alcohol via a [2, 3]-sigmatropic rearrangement involving an intermediate allylic sulfoxide and sulfenate ester. Staudinger reaction of the *o*-azido group and hydrolysis of the intermediate iminophosphorane gave the corresponding *N*-(*o*-aminobenzenesulfonyl)-1,2-amino alcohols. Fmoc protection at nitrogen, oxidation of the alcohol, and Fmoc deprotection furnished directly the 1,2,5-benzothiadiazepine 1,1-dioxides in 57–69% yield. An alternative method which uses triazene chemistry is also presented, but was consistently lower yielding. A second route to 1,2,5-benzothiadiazepine 1,1-dioxides using 2-nitrobenzenesulfonamide as the dienophile precursor proceeded without incident to give *N*-(*o*-nitrobenzenesulfonyl)-1,2-amino ketones which underwent reductive cyclisation to furnish the target heterocycle.

Keywords: Azide; 1,2-Thiazine 1-oxide; Benzodiazepine; Benzothiadiazepine; Allylic sulfoxide; *N*-sulfinylamine

1. Introduction

The synthesis and biological applications of the 1,4-benzodiazepine pharmacophore **1** continue to attract considerable attention in the literature [1–8]. The related 1,2,5-benzothiadiazepine 1,1-dioxides **2**, however, have been subject to much less scrutiny [9–12]. Early interest in 1,2,5-benzothiadiazepine 1,1-dioxides was inspired by their potential use as CNS active compounds [13–14]. More recently it has been shown that, whilst 1,2,5-benzothiadiazepines continue to attract attention as CNS active antidepressives [15–17], they have also exhibited activity as antiarrhythmic agents [18], as inhibitors of metalloproteinase and farnesyl protein transferases [19–21], and as potent tumour necrosis factor-α (TNF-α) converting

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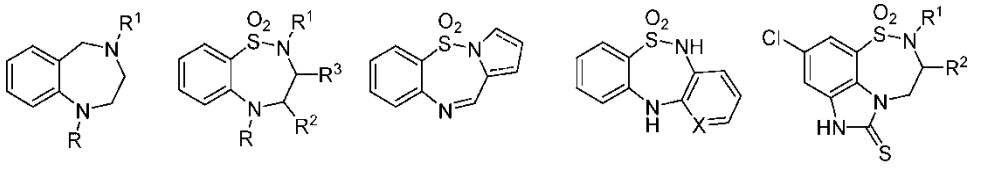
enzyme (TACE) inhibitors [22]. Tricyclic 1,2,5-benzothiadiazepines have attracted particular attention as non-nucleosidic reverse transcriptase inhibitors (NNRTIs) [23–28], a class of compounds that includes the pyrrolo fused system **3** [23–25] and other tricycles such as the heterocycle system **4**, where the latter is the sulfonamide analogue of the well known class of NNRTIs that includes the clinically used nevirapine [26–28]. Benzothiadiazepine analogues **5** of the anti-HIV drug TIBO with specific anti-HIV type 1 activity have also been reported [29] (figure 1). Finally, it is of note that the pyrrolo fused 1,2,5-benzothiadiazepines **3** have also attracted attention [30–32] as sulfonamide analogues of the minor groove DNA-interactive antitumour antibiotic natural and synthetic pyrrolobenzodiazepines [33].

The synthetic routes to the 1,2,5-benzothiadiazepine 1,1-dioxide nucleus include many approaches to the pyrrolobenzothiadiazepines **3** which proceed via 3,4- or 4,5-bond formation of the 1,2,5-benzothiadiazepine ring. These include reductive cyclisation of (2-nitrobenzenesulfonyl)-1*H*-pyrrole derivatives [23, 34], the cyclisation of 1-(2-formamidobenzenesulfonyl)pyrrole with phosphorus oxychloride [30, 34], the reaction of 2-(1*H*-pyrrol-1-yl)benzenesulfonamide with triphosgene [35, 36], the cyclisation of 1-(2-amino-5-chlorobenzenesulfonyl)pyrrole-2-carbohydrazide with loss of hydrazine [37], the cyclisation of 1-(2-fluorobenzenesulfonyl)-1*H*-pyrrole-2-carboxyamides [23], and the reaction of 1-(2-aminobenzenesulfonyl)pyrrole with ethyl glyoxylate [14]. Approaches to simple bicyclic 1,2,5-benzothiadiazepine 1,1-dioxides **2** include synthesis by ring expansion of 1,2,4-benzothiadiazines [38], 1,2-bond formation by intramolecular sulfonamide formation [39, 40], and 2,3-bond formation by intramolecular elimination of ethanol from N-β, β-diethoxyethyl-*N*-alkylanilines [41]. 4,5-Bond formation is a common approach to this system, and has been achieved by cyclisation of 2-(2-aminobenzenesulfonamido) propanoic acid [25]; by reductive cyclisation of 2-nitro-ω-phenacylbenzenesulfonamide [42]; by the use of 2-*N*-[(2-aminobenzenesulfonyl)methylamino]acrylate in an intramolecular Michael reaction [43]; via the use of an intramolecular aza-Wittig reaction [44]; via the ozonolysis and subsequent ring closure of *N*-(2-nitrobenzenesulfonyl) *N*-allylic systems [22]; and from the cyclisation of *N*-(2-aminobenzenesulfonyl) *N*-ethylbromo systems [22]. 5,6-Bond formation by intramolecular S_NAr reaction has also been reported [23].

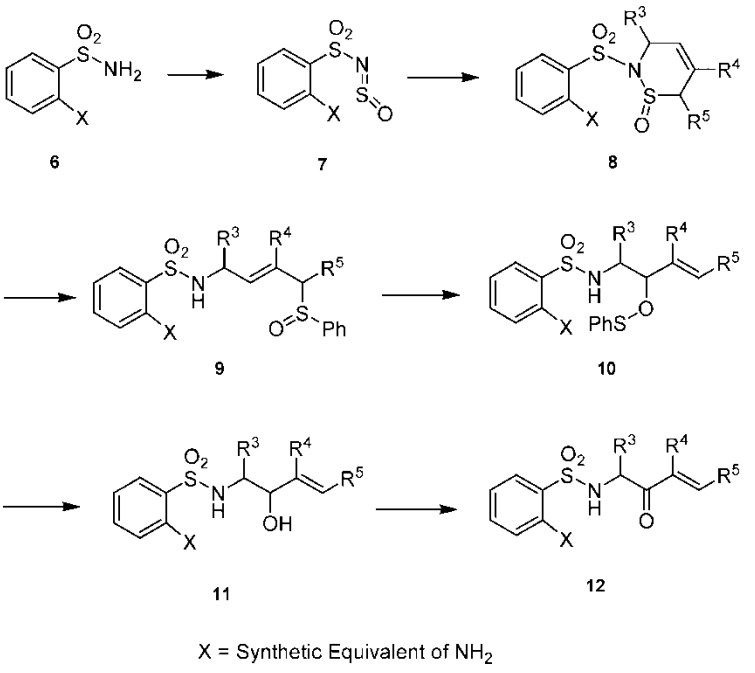
In the current paper, we report a new approach to the 1,2,5-benzothiadiazepine 1,1-dioxide nucleus that begins with a 1,3-diene. Our methodology is the only route that allows this important heterocyclic system to be accessed from dienes, and also provides access to hitherto unreported 1,2,5-benzothiadiazepines.

As part of an ongoing programme of work directed towards the use of 1,2-thiazine 1-oxides as building blocks in heterocyclic synthesis, we have already reported routes to 1,4-benzodiazepines [7, 44] and isoxazolo-fused benzothiazines [45]. Herein we report the conversion of 1,2-thiazine 1-oxides into a series of 1,2,5-benzothiadiazepine 1,1-dioxides. Our original plan is shown in scheme 1. Hence, the 1,2-thiazine 1-oxides **8** (X = synthetic equivalent of NH_2) that are central to our methodology would be accessible from a hetero-Diels-Alder reaction involving the *N*-sulfinylamine dienophiles **7** which are in turn easily



1 **2** **3** **4**, X = CH or N **5**

Figure 1. Examples of some important benzothiadiazepines.

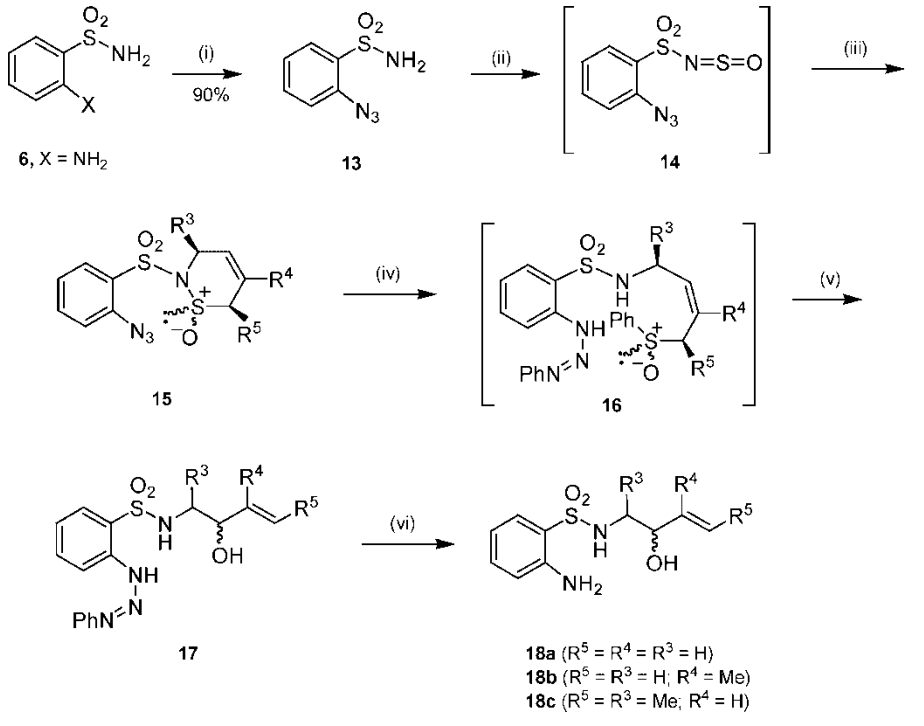


SCHEME 1 Planned route to 1,2,5-benzothiadiazepines.

available from the action of thionyl chloride upon the benzenesulfonamides **6**. Subsequent ring opening of the 1,2-thiazine 1-oxides **8** would give an allylic sulfoxide **9** which is ideally set up for a [2, 3]-sigmatropic, Evans-Mislow, rearrangement [46–53]. Desulfurisation of the resultant sulfenate ester **10** and oxidation of the alcohol **11** should then form the ketone **12**, which is the precursor for an envisaged straightforward cyclisation into the 1,2,5-benzothiadiazepine nucleus **2**. We present the results of this endeavour herein and report the successful synthesis of the alcohols **11** ($X = NH_2$; R^3, R^4, R^5 = Me/H) from 2-aminobenzenesulfonamide (**6**, $X = NH_2$) via selective functionalization of the sulfonamide nitrogen in 58 to 63% overall yield. The successful conversion of the alcohols **11** ($X = NH_2$; R^3, R^4, R^5 = Me/H) into the 1,2,5-benzothiadiazepine 1,1-dioxide nucleus is also discussed. This paper also presents a concise second route to the 1,2,5-benzothiadiazepine 1,1-dioxide nucleus which relies upon the conversion of 2-nitrobenzenesulfonamide (**6**, $X = NO_2$) into 1,2,5-benzothiadiazepine 1,1-dioxides via alcohols **11** ($X = NO_2$; R^3, R^4, R^5 = Me/H) using a similar strategy.

2. Results and discussion

The *N*-sulfinyl group that we required as the dienophile is best accessed via sulfinylation [48–53] of the corresponding sulfonamide. We observed that the greater reactivity of the 2-amino nitrogen of 2-aminobenzenesulfonamide (**6**, $X = NH_2$; scheme 2) towards thionyl chloride precluded reaction at the sulfonamide nitrogen in 2-aminobenzenesulfonamide. We elected, therefore, to diazotise the 2-amino nitrogen and convert it into an azide, with a view to the subsequent conversion of the azide back into an amine at a later stage in the synthesis. Thus, diazotisation of 2-aminobenzenesulfonamide **6** under standard conditions (5M HCl, $NaNO_2$, 0 °C) followed by reaction with sodium azide gave a reproducible 90% yield of 2-azidobenzenesulfonamide **13**, as shown in scheme 2. Reaction of compound **13** with thionyl



SCHEME 2 Synthesis of key intermediate 18 via a triazene. Reaction conditions: (i) HCl(aq.), $NaNO_2$, 0 °C; NaN_3. (ii) $SOCl_2$ (1.5 equiv.), benzene, reflux, 72 hours; or $SOCl_2$, pyridine, THF, room temperature, 3–4 hours. (iii) $R^3CH{=}CH\text{-}CR^4{=}CHR^5$, THF, 25 °C, 16 hours. (iv) PhMgBr (2 equiv.), THF, −40 °C, 2 hours; NH_4Cl(aq.). (v) piperidine (5 equiv.), anhydrous MeOH, 60 °C, 12 hours (inert atmosphere) [54–56]. (vi) MeOH (wet), reflux, 5 hours (open air).

chloride gave the *N*-sulfinyl dienophile **14** which was noted to be unstable upon exposure to the moisture in air, and was hence generated and used *in situ*. Hetero Diels-Alder reaction [48–53] of the *N*-sulfinyl dienophile **14** gave the 2-(*o*-azidobenzenesulfonyl)-1,2-thiazine 1-oxides **15a-c** in ∼80% yield from compound **13** (see table 1) after chromatography. Compound **15c** was isolated as a single diastereoisomer with "cis" R^3/R^5 stereochemistry in line with that expected from the (*E*, *E*)-diene that was used. The stereochemistry at sulfur was not determined due to the fact that this chiral centre was soon to be lost (see below). The treatment of 2-(*o*-azidobenzenesulfonyl)-1,2-thiazine 1-oxides **15** with an excess of PhMgBr followed by aqueous work-up, and then [2,3]-sigmatropic rearrangement/piperidine mediated desulfurisation [54–56] of the intermediate allylic sulfoxides **16** (scheme 2) gave the (1,3-diaryl triazenyl) allylic alcohols **17** in 59–67% yield starting from the 1,2-thiazine 1-oxides **15** (see table 1). The triazene moiety arises as the result of the ring opening of the thiazine 1-oxide with PhMgBr accompanied by the expected [57] reaction of PhMgBr at the azide group to form the triazene. The treatment of the triazenes **17** with boiling aqueous methanol gave the corresponding amines **18** in 60 to 70% yield, a hydrolysis of triazenes which has parallels in the literature [58–61].

The relative stereochemistry of compounds **17c** and **18c** (R^3 = Me) was not determined as, at the next stage, the alcohol chiral centre was to be oxidised. It is of interest to note, however, that others have reported that such reactions proceed with a high degree of stereoselectivity

Table 1. % Yields for isolated, purified products.

Entry	R^3	R^4	R^5	% yield **15** (scheme 2) (from **13**)	% yield **17** (scheme 2) (from **15**)	% yield **21** (scheme 3) (from **15**)	% yield **18** (scheme 3) (from **21**)
a	H	H	H	82	67	99	86
b	H	Me	H	78	64	>99	89
c	Me	H	Me	80	59	>99	82

when performed with other substrates [48, 49, 51–53], a point reflected by the fact that we found compounds **17c** and **18c** to be single diastereoisomers. In the one situation where it is appropriate, i.e. also for compounds **17c** and **18c** ($R^4 = H$, $R^5 = Me$), the alkene geometry was found to be (*E*). This can be explained by invoking a 5-membered ring envelope transition state for the [2, 3]-sigmatropic rearrangement, in which the methyl group that occupies position 6 (see figure 2) in the allylic sulfoxide **16c** is in a pseudo-equatorial position leading to (*E*)-alkene geometry in the intermediate sulfenate ester **19**, geometry which is carried through to compounds **17c** and **18c**.

Using the procedure shown in scheme 2, the highest overall yield that was obtained for compound **18** was that for **18a** ($R^3 = R^4 = R^5 = H$), which was obtained in only 34% yield from 2-aminobenzenesulfonamide **6**. An improved procedure for the conversion of the 2-(*o*-azidobenzenesulfonyl)-1,2-thiazine 1-oxides **15** into the desired amines **18** was therefore sought.

Our improved procedure is set out in scheme 3. The reaction of the azide group in compounds **15** with triphenylphosphine resulted in a quantitative Staudinger reaction [62] to give the iminophosphoranes **20**. The *in situ* hydrolysis [63–66] of the iminophosphoranes **20** with wet THF at reflux gave the 2-(*o*-aminobenzenesulfonyl)-1,2-thiazine 1-oxides **21a–c** in near quantitative yields from the azides **15** (see table 1) after column chromatographic removal of triphenylphosphine oxide. It is noteworthy that these hydrolytic conditions were selective for the iminophosphorane group, and that no competing hydrolysis (see later – scheme 6) of the 1,2-thiazine 1-oxide rings was observed. In the next step, ring opening of the thiazine 1-oxides **21** with PhMgBr gave the phenyl allylic sulfoxides **22**. Conversion of the crude phenyl allylic sulfoxides **22** into the desired *N*-(*o*-aminobenzenesulfonyl)-1,2-vicinal amino alcohols **18** was best achieved by treatment with hot methanolic trimethyl phosphite, a process which occurs via a [2, 3]-sigmatropic rearrangement to give the intermediate sulfenate esters

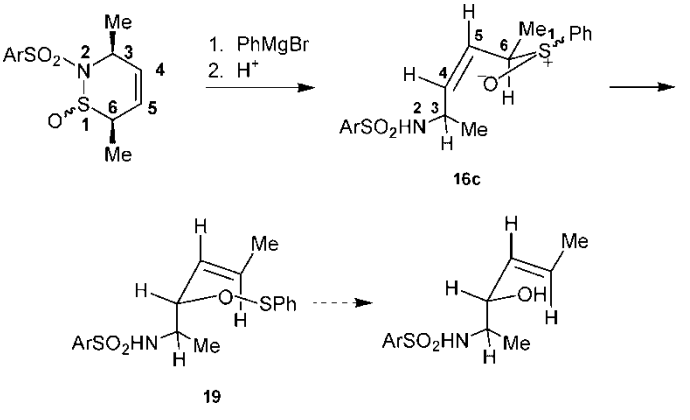
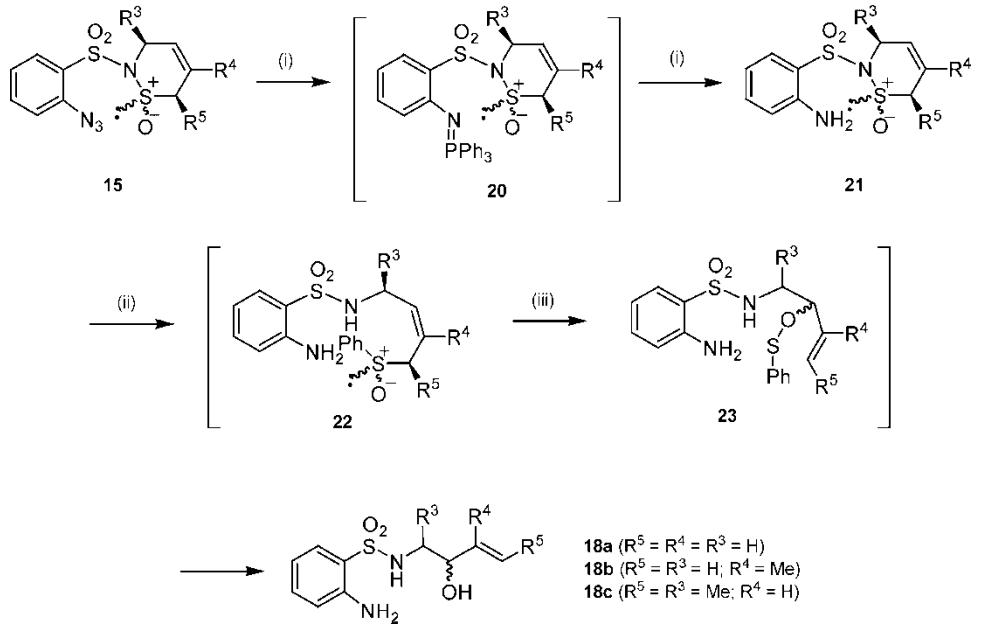


Figure 2. Origin of (E)-alkene geometry.



SCHEME 3 Synthesis of key intermediate 18 using iminophosphoranes. Reaction conditions: (i) PPh_3 (1 equiv.), THF, 25 °C, 3–4 hours (inert atmosphere), then H_2O (8 equiv.), THF, reflux, 15–20 hours (open air). (ii) PhMgBr (2 equiv.), THF, −40 °C, 2 hours; NH_4Cl(aq.). (iii) $P(OMe)_3$, MeOH, 60 °C, 10–15 hours.

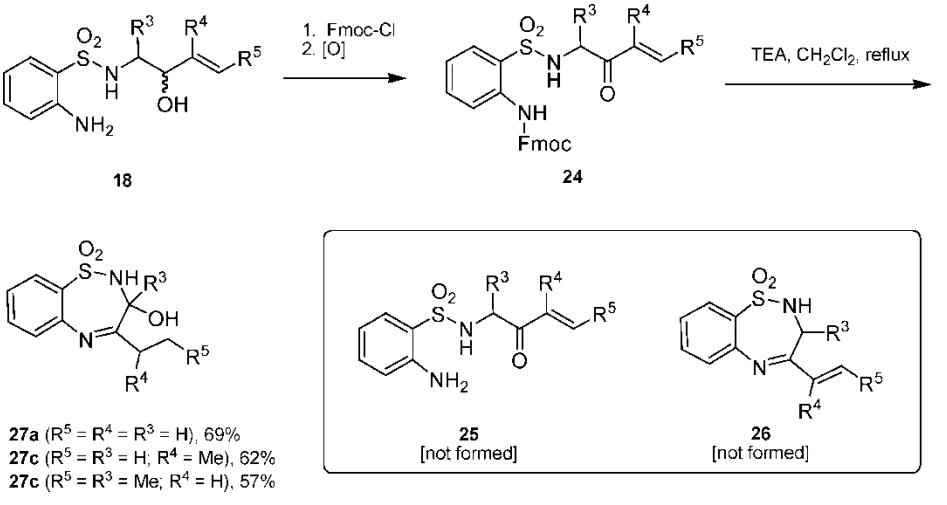
23, which then undergo desulfurisation with the trimethyl phosphite [46–53]. Products **18a–c** were obtained in 82–89% yield from the 2-(*o*-aminobenzenesulfonyl)-1,2-thiazine 1-oxides **21** (see table 1). The next step in the sequence was to be an alcohol oxidation, and hence the relative stereochemistry of the two chiral centres in compound **18c** ($R^4 = H$, $R^5 = R^3 = Me$) was not determined, but it was again noted (see above) to be a single diastereoisomer, as expected [48, 49, 51–53]. Compound **18c** was also noted to have (*E*)-alkene geometry, as discussed above. By this procedure, the highest yield that was obtained for this multi-reaction sequence was again that of compound **18a** ($R^3 = R^5 = R^4 = H$), which was now obtained in 63% overall yield starting from 2-aminobenzenesulfonamide **6**. Compounds **18b** and **18c** were obtained in similarly acceptable overall yields of 62% and 58%, respectively, from 2-aminobenzenesulfonamide **6**.

With a higher yielding and reproducible synthesis of compounds **18a–c** now in hand, we next set about to convert them into the desired 1,2,5-benzothiadiazepine 1,1-dioxides, a process that we anticipated would be trivial. In the event, all attempts to affect the oxidation of the *N*-(*o*-aminobenzenesulfonyl)-1,2-amino alcohols **18a–c** into the corresponding ketones proved unsuccessful under a variety of conditions (for example, Dess-Martin, Swern, TPAP, Corey's reagent, MnO_2, etc), possibly due to a competing reaction at the primary amine. Fortunately, Fmoc protection of the primary amine group (72–81%) allowed the successful oxidation (Dess-Martin, 76–85%) to give the Fmoc protected derivatives **24a–c**, as shown in scheme 4. Standard Fmoc deprotection methods (using secondary amines such as piperidine, diethylamine and dicyclohexylamine) resulted in a multi-spot TLC profile in all cases from which the only identifiable products implied that the amine had undergone Michael addition to the α, β-unsaturated ketone moiety. Such a reaction has been noted by other workers whilst attempting to remove Fmoc with piperidine in the presence of a Michael acceptor [43]. We

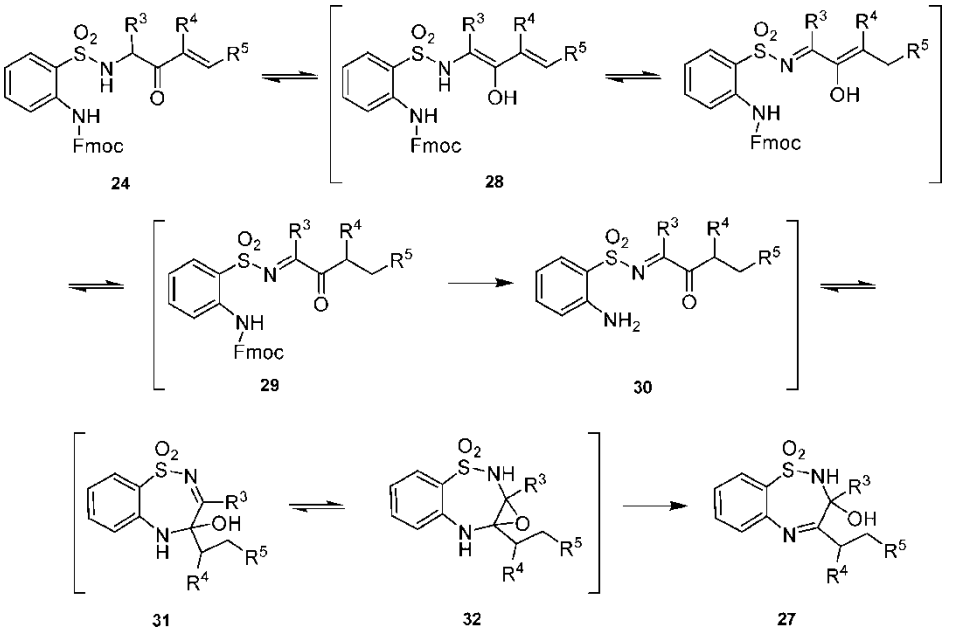
therefore found that a tertiary amine base, triethylamine (TEA), could be used to bring about the removal of Fmoc. These conditions also turned out to be rigorous enough to bring about cyclisation. Thus, treatment of the Fmoc protected ketone derivatives **24a–c** with excess TEA in anhydrous dichloromethane at reflux resulted in the complete disappearance by TLC of the starting material after 15 hours and in the isolation, in each case, of a major new product. The new products were not the deprotected compounds **25** (scheme 4), nor the expected cyclisation products **26**, but were in fact the 3-hydroxy-1,2,5-benzothiadiazepines **27a–c** which were isolated in yields of 57–69%.

With regards to a possible mechanism, it is plausible that the 3-hydroxy-1,2,5-benzothiadiazepines **27** may arise as a result of a series of tautomerisms in starting material **24** to give enol tautomer **28**, followed by the formation of tautomer **29** as shown in scheme 5. Deprotection of tautomer **29** then produces the corresponding amine **30**. Clearly, the exact sequence of events leading to intermediate **30** could be ordered differently so that deprotection occurs first and is followed by the tautomerism sequence. In any event, cyclisation of intermediate **30** would give the carbinolamine **31** which could then give the isolated product **27**, possibly via an intramolecular process such as that involving the intermediate epoxide **32**, as outlined in scheme 5. Alternatively, loss of water across the C4–N5 bond of compound **31**, and the subsequent intermolecular re-addition of water across the N2–C3 double bond of the sulfonimine, would give the isolated product **27**.

In the final part of this work, as shown in scheme 6, we investigated the use of 2-nitrobenzenesulfonamide as a precursor for a shorter synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides. In this respect, we were surprised to find that, whilst we were able to convert 2-nitrobenzenesulfonamide into the dienophile **33** and isolate the Diels-Alder adduct **34c** derived from hexadiene, we were unable to isolate the butadiene or isoprene adducts **34a** and **34b**. This was due to their ready conversion into the corresponding homoallylic sulfonamides **36** (R^4 = H or Me) in the presence of atmospheric moisture. The formation of homoallylic sulfonamides **36** is due to attack of water at the 1,2-thiazine sulfur atom in compounds **34a** and **b**, followed by ring opening of the 1,2-thiazine to give an allylic sulfinic acid **35** with subsequent retro-ene loss of SO_2, an overall process that has precedent in the literature [48–53]. We believe that the presence of a methyl group at the 6-position of the 1,2-thiazine ring in the hexadiene adduct **34c** (R^5 = Me) offers sufficient steric hindrance to prevent the initial



SCHEME 4 Synthesis of 3-hydroxy-1,2,5-benzothiadiazepines.

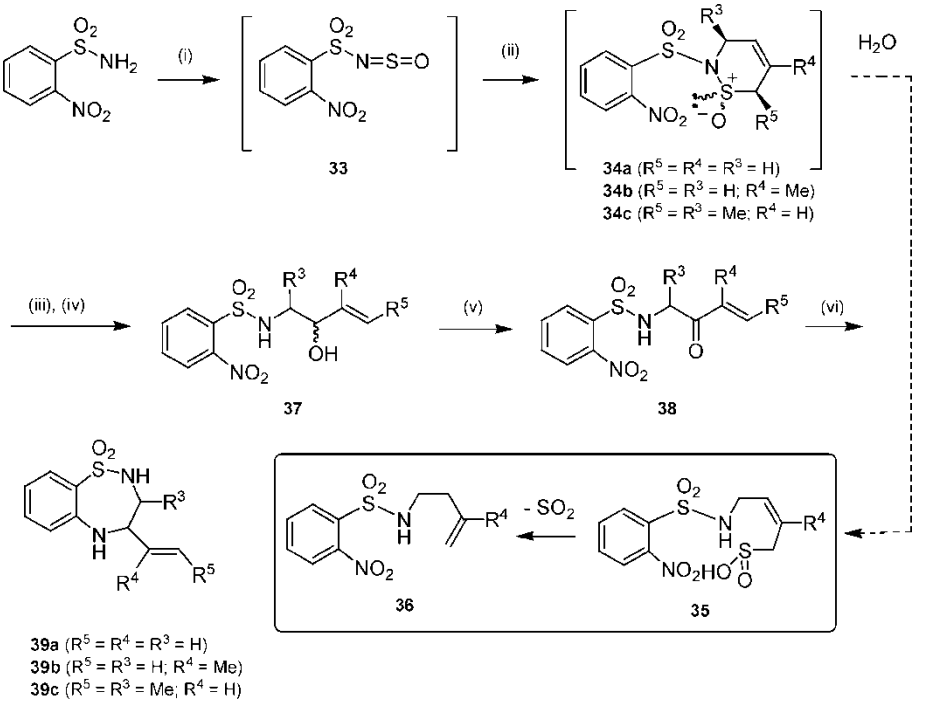


SCHEME 5 Suggested mechanism for the formation of 3-hydroxy-1,2,5-benzothiadiazepines 27.

attack of water at sulfur, hence allowing this adduct to be isolated, whereas adducts **34a** and **b** ($R^5 = H$) are able to accommodate ready access of water to the sulfur and can thus go on to produce the homoallylic sulfonamides **36**. Hexadiene adduct **34c** was isolated in 60% yield and was converted into the alcohol **37c** in 89% yield and thence into the corresponding ketone **38c** in 84% yield, again with the expected (see above) (*E*)-alkene geometry, as shown in scheme 6. The treatment of this ketone with zinc in acetic acid gave access to the 4-alkenyl-1,2,5-benzothiadiazepine 1,1-dioxide **39c** in 45% yield. Interestingly, we were able to show that the air sensitive isoprene and butadiene adducts **34a** and **34b** could be converted *in situ* into the alcohols **37a** and **37b** using the $PhMgBr/P(OMe)_3$ sequence in overall yields of 38% and 45%, respectively, for the four step process from 2-nitrobenzenesulfonamide. The same '*in situ*' process when applied to the hexadiene system gave another method for accessing the alcohol **37c** which was obtained in 44% overall yield for the four steps from 2-nitrobenzenesulfonamide. Finally, oxidation of alcohols **37a** and **b** was achieved in yields of 78% and 89% to give the ketones **38a** and **b**. Ring closure using zinc in acetic acid gave the 4-alkenyl-1,2,5-benzothiadiazepine 1,1-dioxides **39a** and **39b** in 50% and 49% yields, respectively.

3. Summary

In conclusion, two efficient entries (3 examples of each) into the 1,2,5-benzothiadiazepine 1,1-dioxide system have been reported which rely upon the synthesis of *N*-(*o*-aminobenzenesulfonyl)-1,2-vicinal amino alcohols or *N*-(*o*-nitrobenzenesulfonyl)-1,2-vicinal amino alcohols from 1,2-thiazine 1-oxides, which are derived in turn from 2-aminobenzenesulfonamide and 2-nitrobenzenesulfonamide, respectively. A hetero-Diels-Alder reaction between a diene and a *N*-sulfinyl dienophile was used to install the 1,2-thiazine



SCHEME 6 1,2,5-Benzothiadiazepines from 2-nitrobenzenesulfonamide. Reaction conditions: (i) $SOCl_2$, pyridine, THF or $SOCl_2$ (1.5 equiv.), benzene, reflux, 72 hours. (ii) diene. (iii) PhMgBr, THF, −40 °C then H_2O. (iv) $P(OMe)_3$, MeOH, heat. (v) Dess-Martin periodinane. (vi) Zn/AcOH, reflux.

1-oxide grouping which, after conversion into an allylic sulfoxide, underwent a [2, 3]-sigmatropic rearrangement and desulfurisation to produce the 1,2-amino alcohol functionality. For the 2-aminobenzenesulfonamide series, the conversion of the *o*-amino group into an azide allowed the selective functionalization of the sulfonamide nitrogen. The azide could be converted back into the amine very efficiently via the hydrolysis of an intermediate iminophosphorane, or, less efficiently, via the hydrolysis of an intermediate triazene. The *N*-(*o*-aminobenzenesulfonyl)-1,2-vicinal amino alcohols so obtained proved to be useful precursors for the synthesis of 3-hydroxy substituted 1,2,5-benzothiadiazepine 1,1-dioxides. For the 2-nitrobenzenesulfonamide series, the Diels-Alder–[2, 3]-sigmatropic rearrangement – desulfurisation sequence gave *N*-(*o*-nitrobenzenesulfonyl)-1,2-vicinal amino alcohols which served as useful precursors for the synthesis of 4-alkenyl substituted 1,2,5-benzothiadiazepine 1,1-dioxides.

4. Experimental section

4.1 *General considerations*

All starting materials and reagents were used as commercially available. Pyridine, triethylamine, piperidine, diisopropylamine, and *N*,*N*-diisopropylethylamine, were dried over 4 Å molecular sieves prior to use. Solvents for chromatography were of analytical grade.

Petroleum ether used for chromatography was of the 40–60 °C boiling point range. Anhydrous grade solvents were used as supplied, without additional drying, except where stated. Unless otherwise stated, all reactions were conducted using oven-dried glassware under a positive pressure of dry, oxygen-free nitrogen. All reactions were monitored by thin-layer chromatography using aluminium plates coated with silica gel with F_{254} fluorescent indicator. Various mixtures of petroleum ether (40–60 °C) and ethyl acetate were used as the eluent and visualisation of the plates was achieved using ultraviolet light and/or vanillin stain. Flash column chromatography was performed using flash grade silica gel (70–230 mesh; 60 Å) using the eluent described in the experimental protocol.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 or Bruker AC-250 spectrometer operating at 400 MHz (or 100 MHz) and 250 MHz (or 63 MHz) frequency, respectively. Coupling constants (J) are reported in Hertz (Hz) and resonances are designated as follows: singlet (*s*); doublet (*d*); triplet (*t*); quartet (*q*); quintet (*quint*). Broad signals in ^{1}H NMR are denoted as '*br*' and signals corresponding to quaternary carbon atoms in ^{13}C NMR are indicated as '*q*'. Low resolution mass spectra (LRMS) were recorded on a Micromass Quattro II Triple Quadrupole or a VG Micromass 7070 H mass spectrometer operating at a positive ion mode under electron impact (EI), chemical ionisation (CI), or electrospray ionisation (ESI) methods. Molecular ions are reported as their mass, with the percentage abundance quoted in brackets. High resolution mass spectra (HRMS) were recorded on a Finnegan MAT 900 XTL instrument operated by the EPSRC National Mass Spectrometry service at the University of Wales Swansea, UK, and are reported for compounds of >99% purity (NMR) which were single spot pure by TLC. Infrared spectra (IR) were recorded on a Perkin Elmer Paragon 1000 FT-IR instrument as thin films between NaCl plates (oils) or as KBr disks (solids). Absorptions are listed as wavenumber (cm^{-1}), with their absorption intensity indicated parenthetically as broad (*b*), strong (*s*), medium (*m*) or weak (*w*).

4.2 *Synthesis of 2-(o-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides (15)*

4.2.1 General procedure, Method A. To a suspension of *o*-azidobenzenesulfonamide (**13**; 5–8 mmol, 1.0 eq) in anhydrous benzene (30–50 ml) [CAUTION: SUSPECTED CARCINOGEN – see Method B for an alternative] was added, under an atmosphere of dry nitrogen, thionyl chloride (1.5 eq), and the whole was heated at reflux in an oil bath for 3 days (~72 hours), or until the sulfonamide had completely dissolved. The reaction mixture was allowed to cool to room temperature and the solvent and excess thionyl chloride were removed *in vacuo* to yield the *N*-sulfinyl-*o*-azidobenzenesulfonamide (**14**) as a brown oil. To the crude *N*-sulfinyl-*o*-azidobenzenesulfonamide (**14**) in anhydrous tetrahydrofuran (20–30 ml) was added, under nitrogen, the diene (1.6 eq), and the reaction mixture was stirred at room temperature for 6–16 hours, whilst being monitored by TLC. After completion of the reaction, the solvent was removed *in vacuo* and the crude product was purified by flash silica column chromatography (eluent: PE:EtOAc/1:1) to yield the 2-(*o*-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides (**15**), as follows:

2-(o-Azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (**15a**) was obtained as a yellow solid (1.235 g, 82% yield) from *o*-azidobenzenesulfonamide (**13**; 1.000 g, 5.05 mmol) and 1,3-butadiene (large excess, ~10 eq), mp: 122–124 °C.

δ_H (400 MHz, $CDCl_3$): 3.45 (1 H, ddd, *J* 16.5, 6.2, 2.3, CH_2S=O), 3.61 (1 H, ddd, *J* 16.5, 5.1, 2.5, CH_2S=O), 3.83 (1 H, ddd, *J* 17.4, 5.2, 2.3, CH_2N), 4.11–4.17 (1 H, m, CH_2N), 5.73–5.79 (1 H, m, HC=C*H*), 5.96–6.01 (1 H, m, *H*C=CH), 7.28 (1 H, td, *J* 7.8, 0.9, Ar*H*), 7.34 (1 H, dd, *J* 8.0, 0.8, Ar*H*), 7.66 (1 H, td, *J* 7.8, 1.5, Ar*H*), 8.01 (1 H, dd, *J* 8.0, 1.5, Ar*H*). δ_C (100 MHz, $CDCl_3$): 39.0 (*C*H_2), 50.6 (*C*H_2), 114.6 (*C*H), 120.3 (*C*H), 124.3 (*C*H),

124.6 (*C*H), 127.7 (q), 131.6 (*C*H), 135.1 (*C*H), 139.1 (q). υ_{max} (cm^{-1}): 3010 (w), 2919 (w), 2133 (s), 1575 (m), 1470 (s), 1433 (m), 1352 (s), 1282 (s), 1170 (s), 1103 (s), 1060 (s), 1003 (m), 868 (m), 771 (s), 653 (m). EI+ mass spectrum (m/z, %): 298 ($[M]^+$, 4%), 282 ($[M–O]^+$, 1%), 270 ($[M–N_2]^+$, 2%), 250 ($[M–SO]^+$, 3%), 172 (5%), 156 (10%), 116 (25%), 104 (20%), 90 (40%), 76 (35%), 64 (50%), 54 (30%), 39 (100%). CI+ mass spectrum (m/z, %): 316 ($[M+NH_4]^+$, 100%), 299 ($[M+H]^+$, 6%). HRMS (ESI+): found $[M+NH_4]^+$ 316.0534, $C_{10}H_{10}N_4O_3S_2$ requires 316.0538. C, H, N(%): found C 40.4, H 3.4, N 18.6; $C_{10}H_{10}N_4O_3S_2$ requires C 40.3, H 3.4, N 18.8.

2-(o-Azidobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (**15b**) was obtained as a yellow solid (1.845 g, 78% yield) from *o*-azidobenzenesulfonamide (**13**; 1.500 g, 7.57 mmol) and isoprene (1.21 ml, 12.11 mmol), mp: 146–148 °C.

δ_H (400 MHz, $CDCl_3$): 1.80 (3 H, s, C*H*$_3$), 3.23 (1 H, dd, *J* 16.2, 1.8, C*H*$_2$S=O), 3.57–3.62 (1 H, dm, *J* 16.2, C*H*$_2$S=O), 3.75–3.82 (1 H, dm, *J* 17.0, C*H*$_2$N), 4.05–4.10 (1 H, dm, *J* 17.0, C*H*$_2$N), 5.66 (1 H, d, *J* 1.9, MeC=C*H*), 7.24 (1 H, t, *J* 7.7, Ar*H*), 7.32 (1 H, d, *J* 8.1, Ar*H*), 7.64 (1 H, td, *J* 7.8, 1.4, Ar*H*), 7.99 (1 H, dd, *J* 8.0, 1.4, Ar*H*). δ_C (100 MHz, $CDCl_3$): 24.2 (*C*H_3), 39.3 (*C*H_2), 54.3 (*C*H_2), 117.6 (*C*H), 120.2 (*C*H), 122.6 (q), 124.5 (*C*H), 127.7 (q), 131.5 (*C*H), 135.1 (*C*H), 139.0 (q). υ_{max} (cm^{-1}): 3011 (w), 2916 (w), 2134 (s), 1575 (m), 1473 (s), 1444 (m), 1350 (s), 1293 (m), 1172 (s), 1103 (s), 1064 (m), 1010 (w), 832 (m), 757 (s), 655 (m). EI+ mass spectrum (m/z, %): 312 ($[M]^+$, 2%), 296 ($[M–O]^+$, 1%), 284 ($[M–N_2]^+$, 3%), 264 ($[M–SO]^+$, 1%), 183 (5%), 171 (10%), 156 (15%), 130 (10%), 108 (15%), 104 (15%), 90 (55%), 84 (45%), 76 (35%), 68 (100%). CI+ mass spectrum (m/z, %): 330 ($[M+NH_4]^+$, 97%), 313 ($[M+H]^+$, 15%), 284 ($[M–N_2]^+$, 90%). HRMS (ESI+): found $[M+H]^+$ 313.0425, $C_{11}H_{12}N_4O_3S_2$ requires 313.0429. C, H, N(%): found C 42.4, H 3.7, N 17.8; $C_{11}H_{12}N_4O_3S_2$ requires C 42.3, H 3.9, N 17.9.

2-(o-Azidobenzenesulfonyl)-3,6-dihydro-3,6-dimethyl-1,2-thiazine 1-oxide (**15c**) was obtained as a yellow solid (1.580 g, 80% yield) from *o*-azidobenzenesulfonamide (**13**; 1.200 g, 6.054 mmol) and (*E, E*)-2,4-hexadiene (1.10 ml, 9.69 mmol), mp: 137–139 °C.

δ_H (250 MHz, $CDCl_3$): 1.27 (3 H, d, *J* 7.0, C*H*$_3$CHS=O), 1.46 (3 H, d, *J* 7.4, C*H*$_3$CHN), 3.29–3.41 (1 H, m, MeC*H*S=O), 4.55–4.68 (1 H, m, MeC*H*N), 5.45 (1 H, ddd, *J* 11.0, 2.5, 1.5, HC=C*H*), 5.91 (1 H, dt, *J* 11.0, 3.2, HC=C*H*), 7.25–7.35 (2H, m, 2xAr*H*), 7.62–7.69 (1 H, m, Ar*H*), 8.06 (1 H, dd, *J* 8.0, 0.9, Ar*H*). δ_C (63 MHz, $CDCl_3$): 15.9 (*C*H_3), 22.2 (*C*H_3), 51.2 (*C*H), 53.3 (*C*H), 119.8 (*C*H), 120.1 (*C*H), 124.8 (*C*H), 129.7 (*C*H), 130.4 (q), 131.1 (*C*H), 135.0 (*C*H), 138.7 (q). υ_{max} (cm^{-1}): 3020 (w), 2929 (w), 2131 (s), 1575 (m), 1472 (s), 1441 (m), 1353 (m), 1262 (s), 1166 (s), 1121 (s), 1060 (m), 1003 (m), 877 (m), 752 (s), 657 (m). EI+ mass spectrum (m/z, %): 327 ($[M+H]^+$, 2%), 310 ($[M–O]^+$, 2%), 298 ($[M–N_2]^+$, 4%), 278 ($[M–SO]^+$, 3%), 208 (10%), 198 (5%), 183 (5%), 171 (10%), 154 (8%), 144 (10%), 105 (15%), 96 (20%), 90 (30%), 82 (100%), 76 (25%), 67 (60%). CI+ mass spectrum (m/z, %): 344 ($[M+NH_4]^+$, 100%), 327 ($[M+H]^+$, 55%), 298 ($[M–N_2]^+$, 20%). HRMS (ESI+): found $[M+H]^+$ 327.0585, $C_{12}H_{14}N_4O_3S_2$ requires 327.0585. C, H, N(%): found C 44.4, H 4.4, N 17.0; $C_{12}H_{14}N_4O_3S_2$ requires C 44.2, H 4.3, N 17.2.

4.2.2 Method B (avoiding the use of benzene). To a solution of *o*-azidobenzenesulfonamide (**13**, ~5–10 mmol, 1.0 eq) and anhydrous pyridine (2.0 eq) in anhydrous tetrahydrofuran (30–60 ml), under an atmosphere of dry nitrogen, was added, dropwise with stirring over a period of 3 hours, a solution of thionyl chloride (1.0 eq) in anhydrous tetrahydrofuran (5–8 ml). Stirring of the reaction mixture was continued for a further 30 minutes, followed by dropwise addition of the appropriate 1,3-diene (1.6 eq), and the whole was allowed to stir at room temperature for 6–16 hours whilst being monitored by TLC. In the case of the

1,3-butadiene adduct (**15a**), the diene was condensed at low temperature (−20 °C) and subsequently added to the mixture, maintaining the low temperature of the reaction for 4–6 hours. After completion of the reaction, the solvent was removed *in vacuo* and the crude product was purified by flash column silica chromatography (eluent PE:EtOAc/1:1). The *2-(o-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides* (**15**) were obtained as follows:

2-(o-Azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (**15a**) was obtained as a yellow solid (0.8720 g, 58% yield) from *o*-azidobenzenesulfonamide (**13**; 1.000 g, 5.05 mmol) and 1,3-butadiene (large excess, ∼10 eq).

2-(o-Azidobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (**15b**) was obtained as a yellow solid (1.512 g, 60% yield) from *o*-azidobenzenesulfonamide (**13**; 1.600 g, 8.07 mmol) and isoprene (1.29 ml, 12.92 mmol).

2-(o-Azidobenzenesulfonyl)-3,6-dihydro-3,6-dimethyl-1,2-thiazine 1-oxide (**15c**) was obtained as a yellow solid (1.720 g, 70% yield) from *o*-azidobenzenesulfonamide (**13**; 1.500 g, 7.57 mmol) and 2,4-hexadiene (1.38 ml, 12.11 mmol). [For full characterization data of these compounds, see Method A, above].

4.3 *Synthesis of (o-aminobenzenesulfonamidyl)alkenols (18)*

4.3.1 Method 1. Synthesis via the triazene route (see scheme 2). Synthesis of [3'-(o-benzenesulfonamidyl)-1'-phenyltriazene] alkenols (17). A solution of phenylmagnesium bromide (3 M in ether, 3.0 eq) was added to a stirred solution of the 2-(*o*-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (**15**; ∼1.0–3.5 mmol, 1.0 eq) in anhydrous tetrahydrofuran (10–20 ml) at −78 °C, under an atmosphere of dry nitrogen. The reaction mixture was kept at low temperature (<−40 °C) for 3–4 hours, whilst being monitored by TLC. Upon completion of the reaction, the mixture was quenched at −20 °C with saturated ammonium chloride solution (15 ml) and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (2 × 20 ml) and the combined organic layers were washed with water (2 × 20 ml) and brine (10 ml). The organic phase was collected, dried ($MgSO_4$), filtered and the solvent evaporated off to yield the phenyl allylic sulfoxide (**16**), which was not purified further. To a solution of the crude allylic sulfoxide (**16**) in anhydrous methanol (10–20 ml) was added anhydrous piperidine (5.0 eq), under an atmosphere of dry nitrogen, and the whole was heated under reflux for a total of 10–15 hours, whilst being monitored by TLC. Upon completion of the reaction, the solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (eluent: PE:EtOAc/5:2) to yield the [3'-(o-benzenesulfonamidyl)-1'-phenyltriazene] alkenols (**17**) as follows:

4-[3'-(o-Benzenesulfonamidyl)-1'-phenyltriazene]-but-1-en-3-ol (**17a**) was obtained as a yellow oil, which solidified to give a waxy solid (0.7770 g, 67% yield), from 2-(*o*-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (**15a**; 1.000 g, 3.35 mmol), mp 172–174 °C.

δ_H (400 MHz, $CDCl_3$): 2.92 (1 H, dd, *J* 12.8, 8.2, CH_2NH), 3.19 (1 H, dd, *J* 12.8, 3.3, CH_2NH), 4.37 (1 H, s, br, C*H*OH), 5.17 (1 H, d, *J* 10.6, HC=CH_2), 5.33 (1 H, d, *J* 17.2, HC=CH_2), 5.81 (1 H, ddd, *J* 16.6, 10.8, 5.6, H_2C=C*H*), 7.11–7.13 (3 H, m, 3 × Ar*H*), 7.25 (2 H, t, *J* 7.7, 2 × Ar*H*), 7.31 (1 H, t, *J* 7.6, Ar*H*), 7.54 (1 H, t, *J* 7.8, Ar*H*), 7.71 (1 H, d, *J* 8.1, Ar*H*), 8.02 (1 H, d, *J* 7.8, Ar*H*). δ_C (100 MHz, $CDCl_3$): 48.7 (*C*H_2), 71.1 (*C*H), 117.0 (*C*H_2), 117.5 (*C*H), 124.9 (*C*H), 125.3 (*C*H), 129.2 (*C*H), 129.3 (*C*H), 129.7 (q), 133.9 (*C*H), 135.4 (q), 136.9 (*C*H), 144.0 (q). υ_{max} (neat oil, cm^{-1}): 3476 (bm), 3291 (m), 3231 (m), 2987 (m), 2928 (m), 2306 (m), 1602 (s), 1527 (m), 1466 (s), 1441 (s), 1421 (s), 1327 (s), 1155 (s), 1126 (m), 1087 (m), 909 (s), 728 (s). EI+ mass spectrum (m/z, %): 346 ($[M]^+$, 1%), 149 (15%), 105 (20%), 91 (20%), 84 (75%), 77 (60%), 69 (35%), 65 (25%), 57 (40%). ESI+ mass

spectrum (m/z, %): 715 ([2M+Na]$^+$, 25%), 693 ([2M+H]$^+$, 2%), 369 ([M+Na]$^+$, 100%), 347 ([M+H]$^+$, 10%). HRMS (ESI+): found [M+H]$^+$ 347.1174, $C_{16}H_{18}N_4O_3S$ requires 347.1178. C, H, N(%): found C 55.4, H 5.4, N 16.4; $C_{16}H_{18}N_4O_3S$ requires C 55.5, H 5.2, N 16.2.

4-[3'-(o-Benzenesulfonamidyl)-1'-phenyltriazene]-2-methyl-but-1-en-3-ol (**17b**) was obtained as a yellow oil which solidified on standing to give a waxy solid (0.3690 g, 64% yield) from 2-(*o*-azidobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (**15b**; 0.5000 g, 1.60 mmol), mp 122–128 °C.

δ_H (400 MHz, $CDCl_3$): 1.67 (3 H, s, C*H*$_3$), 2.80 (1 H, s, br, O*H*), 2.93 (1 H, dd, *J* 12.7, 8.3, C*H*$_2$NH), 3.24 (1 H, dd, *J* 12.7, 3.3, C*H*$_2$NH), 4.26 (1 H, dd, *J* 5.2, 1.6, C*H*OH), 4.90 (1 H, s, MeC=C*H*$_2$), 5.03 (1 H, s, MeC=C*H*$_2$), 6.05 (1 H, s, br, N*H*), 7.19–7.21 (3 H, m, 3 × Ar*H*), 7.28–7.32 (3 H, m, 3 × Ar*H*), 7.55 (1 H, td, *J* 7.8, 1.3, Ar*H*), 7.74 (1 H, d, *J* 8.2, Ar*H*), 8.01 (1 H, dd, *J* 7.9, 1.3, Ar*H*), 11.0 (1 H, s, br, N*H*). δ_C (100 MHz, $CDCl_3$): 18.5 (*C*H$_3$), 47.5 (*C*H$_2$), 73.5 (*C*H), 112.5 (*C*H$_2$), 117.1 (q), 117.4 (*C*H), 123.0 (q), 123.2 (q), 125.1 (*C*H), 125.3 (*C*H), 129.2 (*C*H), 129.4 (*C*H), 133.9 (*C*H), 144.0 (q). υ_{max} (cm^{-1}): 3468 (bm), 3290 (m), 3229 (m), 2987 (m), 2927 (m), 2306 (m), 1602 (s), 1526 (m), 1466 (s), 1441 (s), 1420 (s), 1327 (s), 1154 (s), 1123 (m), 1098 (m), 910 (m), 730 (s). EI+ mass spectrum (m/z, %): 360 ([M]$^+$, 1%), 156 (10%), 105 (25%), 92 (40%), 84 (20%), 77 (100%), 69 (25%), 65 (45%), 57 (25%). ESI+ mass spectrum (m/z, %): 743 ([2M+Na]$^+$, 30%), 721 ([2M+H]$^+$, 5%), 383 ([M+Na]$^+$, 100%), 361 ([M+H]$^+$, 15%). HRMS (ESI+): found [M+H]$^+$ 361.1333, $C_{17}H_{20}N_4O_3S$ requires 361.1334. C, H, N(%): found C 56.9, H 5.8, N 15.2; $C_{17}H_{20}N_4O_3S$ requires C 56.7, H 5.6, N 15.5.

(E)-5-[3'-(o-Benzenesulfonamidyl)-1'-phenyltriazene]-hex-2-en-4-ol (**17c**) was obtained as a yellow waxy solid (0.4740 g, 59% yield) from 2-(*o*-azidobenzenesulfonyl)-3,6-dihydro-3,6-dimethyl-1,2-thiazine 1-oxide (**15c**; 0.7000 g, 2.15 mmol), mp: 149–153 °C.

δ_H (400 MHz, $CDCl_3$): 1.07 (3 H, d, *J* 6.7, C*H*$_3$CHNH), 1.62 (3 H, dd, *J* 6.5, 1.4, C*H*$_3$CH=CH), 3.00 (1 H, s, br, O*H*), 3.34 (1 H, dq, *J* 15.3, 6.4, MeC*H*NH), 3.94 (1 H, t, *J* 6.5, C*H*OH), 5.39 (1 H, ddd, *J* 15.3, 7.3, 1.5, MeHC=C*H*), 5.71 (1 H, dq, *J* 14.9, 6.6, CH=C*H*Me), 5.90 (1 H, s, br, N*H*), 7.13 (1 H, t, *J* 7.1, Ar*H*), 7.16–7.21 (2H, m, 2 × Ar*H*), 7.25–7.30 (3 H, m, 3 × Ar*H*), 7.53 (1 H, td, *J* 7.8, 1.4, Ar*H*), 7.75 (1 H, d, *J* 8.1, Ar*H*), 8.01 (1 H, dd, *J* 7.9, 1.1, Ar*H*), 11.2 (1 H, s, br, N*H*). δ_C (100 MHz, $CDCl_3$): 17.4 (*C*H$_3$), 17.7 (*C*H$_3$), 54.9 (*C*H), 75.7 (*C*H), 117.2 (*C*H), 117.3 (*C*H), 122.7 (q), 125.1 (*C*H), 125.3 (*C*H), 129.1 (*C*H), 129.8 (*C*H), 130.1 (*C*H), 132.3 (q), 133.7 (*C*H), 141.3 (q). υ_{max} (cm^{-1}): 3470 (bm), 3289 (m), 3230 (m), 2987 (m), 2928 (m), 2305 (m), 1601 (s), 1527 (m), 1465 (s), 1441 (s), 1422 (s), 1327 (s), 1155 (s), 1123 (m), 1087 (m), 896 (m), 739 (s). EI+ mass spectrum (m/z, %): 374 ([M]$^+$, 1%), 303 (2%), 149 (15%), 105 (40%), 92 (30%), 84 (65%), 77 (100%), 69 (65%), 65 (35%), 56 (70%). ESI+ mass spectrum (m/z, %): 771 ([2M+Na]$^+$, 25%), 749 ([2M+H]$^+$, 3%), 397 ([M+Na]$^+$, 100%), 375 ([M+H]$^+$, 10%). HRMS (ESI+): found [M+H]$^+$ 375.1486, $C_{18}H_{22}N_4O_3S$ requires 375.1491. C, H, N(%): found C 57.4, H 5.8, N 15.1; $C_{18}H_{22}N_4O_3S$ requires C 57.7, H 5.9, N 15.0.

Synthesis of (o-aminobenzenesulfonamidyl)alkenols (18) from triazenes (17). A solution of the [3'-(*o*-benzenesulfonamidyl)-1'-phenyltriazene] alkenol (**17**) (~0.5–1.5 mmol) in standard laboratory reagent grade methanol was heated at reflux in the open air for a total of 5 hours. The reaction mixture was allowed to cool to room temperature, the solvent was removed *in vacuo* and the crude product was purified by column chromatography (eluent: PE:EtOAc/5:2) to yield the *4-(o-aminobenzenesulfonamidyl)-but-1-en-3-ols* (**18**) in 60–70% yield. As a typical example, *4-(o-aminobenzenesulfonamidyl)-but-1-en-3-ol* (**18a**) was obtained as a yellow oil (0.2450 g, 70% yield) from 4-[3'-(*o*-benzenesulfonamidyl)-1'-phenyltriazene]-but-1-en-3-ol (**17a**; 0.5000 g, 1.44 mmol). [*Data for compounds* (**18a–c**) *were identical to that provided via the more efficient Method 2, details of which are listed immediately below*].

4.3.2 Method 2. Synthesis via the hydrolysis of iminophosphorane (20) (see scheme 3). Synthesis of 2-(o-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides (21). To a solution of the 2-(*o*-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (**15**; ∼3–6 mmol, 1.0 eq) in anhydrous tetrahydrofuran (10–20 ml) was added, dropwise with stirring over a period of 1 hour, a solution of triphenylphosphine (1.0 eq) in anhydrous tetrahydrofuran (5–8 ml) under an atmosphere of dry nitrogen. The mixture was stirred for 3–4 hours, after which analysis by TLC showed a single new spot, assumed to be the 2-[*o*-*N*-(triphenylphosphoranylidene)benzenesulfonyl]-3,6-dihydro-1,2-thiazine 1-oxides (**20**). Water (∼8 eq) was added to the mixture and the whole was heated at reflux in the open air for a total of 15 hours, at which stage TLC showed disappearance of the assumed intermediate (**20**) and the presence of a single new spot together with base-line material which was later identified as triphenylphosphine oxide. The reaction mixture was allowed to cool to room temperature, the solvent was removed *in vacuo* and the crude product was purified by gravity column chromatography on silica (eluent: PE:EtOAc/2:1) to yield the *2-(o-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides* (**21**) as light yellow oils, which darkened on standing and which were used immediately in the next step. Data for samples of compounds (**21a–c**) were as follows:

2-(o-Aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (**21a**) was obtained as a yellow oil (0.900 g, 99%) from 2-(*o*-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (**15a**; 1.000 g, 3.35 mmol).

δ_H (250 MHz, $CDCl_3$): 3.39 (1 H, ddd, *J* 16.5, 6.3, 2.4, CH_2S=O), 3.61 (1 H, ddd, *J* 16.4, 5.2, 2.8, CH_2S=O), 3.80 (1 H, ddd, *J* 17.1, 5.3, 2.3, CH_2N), 3.99–4.10 (1 H, dm, *J* 17.1, CH_2N), 5.12 (2H, s, br, NH_2), 5.71 (1 H, dddd, *J* 12.8, 8.6, 4.5, 2.1, HC=C*H*), 5.92–6.00 (1 H, m, *H*C=CH), 6.72–6.81 (2H, m, 2 × Ar*H*), 7.33 (1 H, td, *J* 7.7, 1.6, Ar*H*), 7.67 (1 H, dd, *J* 8.1, 1.5, Ar*H*). δ_C (63 MHz, $CDCl_3$): 39.0 (*C*H_2), 50.6 (*C*H_2), 114.5 (*C*H), 117.6 (*C*H), 117.7 (q), 118.1 (*C*H), 124.4 (*C*H), 130.1 (*C*H), 135.4 (*C*H), 146.2 (q). ^{31}P spectroscopy showed the sample to be free of phosphorus. υ_{max} (cm^{-1}): 3432 (m), 3339 (m), 2960 (m), 2918 (m), 1617 (s), 1560 (m), 1484 (s), 1454 (m), 1342 (s), 1166 (s), 1075 (s), 1002 (m), 869 (m), 773 (s), 630 (s). EI+ mass spectrum (m/z, %): 273 ($[M+H]^+$, 3%), 272 ($[M]^+$, 15%), 224 ($[M–SO]^+$, 15%), 218 (30%), 172 (5%), 156 (40%), 140 (10%), 116 (10%), 108 (30%), 92 (100%), 65 (80%), 54 (10%). CI+ mass spectrum (m/z, %): 290 ($[M+NH_4]^+$, 100%), 273 ($[M+H]^+$, 60%). HRMS (ESI+): found $[M+H]^+$ 273.0367, $C_{10}H_{12}N_2O_3S_2$ requires 273.0367.

2-(o-Aminobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (**21b**) was obtained as a yellow oil (1.454 g, >99%) from 2-(*o*-azidobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (**15b**; 1.600 g, 5.12 mmol, 1.0 eq).

δ_H (400 MHz, $CDCl_3$): 1.83 (3 H, s, CH_3), 3.22 (1 H, dd, *J* 16.2, 1.9, CH_2S=O), 3.61 (1 H, dt, *J* 16.2, 1.2, CH_2S=O), 3.80 (1 H, ddq, *J* 16.6, 5.8, 2.1, CH_2N), 4.00 (1 H, dt, *J* 16.6, 2.1, CH_2N), 5.14 (2H, s, br, NH_2), 5.67 (1 H, m, MeC=C*H*), 6.75 (1 H, dd, *J* 8.1, 0.6, Ar*H*), 6.80 (1 H, dt, *J* 7.6, 0.8, Ar*H*), 7.35 (1 H, td, *J* 7.7, 1.4, Ar*H*), 7.70 (1 H, dd, *J* 8.1, 1.4, Ar*H*). δ_C (100 MHz, $CDCl_3$): 24.3 (*C*H_3), 39.3 (*C*H_2), 54.3 (*C*H_2), 117.6 (*C*H), 117.8 (*C*H), 117.9 (q), 118.0 (*C*H), 122.6 (q), 130.2 (*C*H), 135.4 (*C*H), 146.1 (q). υ_{max} (cm^{-1}): 3462 (m), 3338 (m), 2961 (m), 2928 (s), 1625 (m), 1598 (m), 1483 (s), 1438 (s), 1343 (s), 1158 (s), 1093 (s), 1027 (w), 927 (m), 758 (s), 668 (s). EI+ mass spectrum (m/z, %): 286 ($[M]^+$, 4%), 238 ($[M–SO]^+$, 8%), 218 (15%), 172 (10%), 156 (30%), 140 (10%), 108 (35%), 92 (100%), 65 (25%). ESI+ mass spectrum (m/z, %): 309 ($[M+Na]^+$, 8%), 287 ($[M+H]^+$, 20%). HRMS (ESI+): found $[M+H]^+$ 287.0524, $C_{11}H_{14}N_2O_3S_2$ requires 287.0524.

2-(o-Aminobenzenesulfonyl)-3,6-dihydro-3,6-dimethyl-1,2-thiazine 1-oxide (**21c**) was obtained as a yellow oil (1.650 g, >99%) from 2-(*o*-azidobenzenesulfonyl)-3,6-dihydro-3,6-dimethyl-1,2-thiazine 1-oxide (**15c**; 1.800 g, 5.52 mmol).

δ_H (250 MHz, $CDCl_3$): 1.41 (3 H, d, *J* 7.0, C*H*$_3$CHS=O), 1.44 (3 H, d, *J* 7.5, C*H*$_3$CHN), 3.42 (1 H, dq, *J* 7.6, 1.9, MeC*H*S=O), 4.33 (1 H, dq, *J* 6.8, 3.4, MeC*H*N), 4.91–4.95 (2H, br, N*H*$_2$), 5.38 (1 H, ddd, *J* 11.0, 2.1, 2.1, HC=C*H*), 5.84 (1 H, ddd, *J* 11.0, 3.3, 3.3, *H*C=CH), 6.75 (1 H, d, *J* 8.3, Ar*H*), 6.78–6.83 (1 H, m, Ar*H*), 7.34 (1 H, td, *J* 7.7, 1.5, Ar*H*), 7.75 (1 H, td, *J* 7.5, 1.5, Ar*H*). δ_C (63 MHz, $CDCl_3$): 15.8 (*C*H$_3$), 22.9 (*C*H$_3$), 50.8 (*C*H), 52.9 (*C*H), 117.8 (*C*H), 118.0 (*C*H), 119.8 (*C*H), 120.8 (q), 129.5 (*C*H), 129.9 (*C*H), 135.1 (*C*H), 145.3 (q). υ_{max} (cm^{-1}): 3476 (w), 3373 (w), 2968 (m), 2928 (m), 1621 (m), 1566 (w), 1483 (s), 1455 (m), 1342 (s), 1157 (s), 1100 (s), 942 (m), 880 (s), 755 (s), 669 (s). EI+ mass spectrum (m/z, %): 300 ($[M]^+$, 2%), 252 ($[M–SO]^+$, 4%), 218 (15%), 172 (4%), 156 (6%), 140 (5%), 108 (20%), 92 (100%), 82 (80%), 77 (20%), 65 (85%). CI+ mass spectrum (m/z, %): 318 ($[M+NH_4]^+$, 70%), 301 ($[M+H]^+$, 40%). HRMS (ESI+): found $[M+H]^+$ 301.0675, $C_{12}H_{16}N_2O_3S_2$ requires 301.0680.

Synthesis of (o-aminobenzenesulfonamidyl)alkenols (18) from compounds (21). A solution of phenylmagnesium bromide (3 M in ether, 2.0 eq) was added to a stirring solution of the 2-(*o*-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (**21**; ~2–5 mmol, 1.0 eq) in anhydrous tetrahydrofuran (10–20 ml) at −78 °C, under an atmosphere of dry nitrogen. The reaction mixture was kept at low temperature (<−40 °C) for 3–4 hours, whilst being monitored by TLC. Upon completion of the reaction, the mixture was quenched at −20 °C with saturated ammonium chloride solution (15 ml) and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (2 × 20 ml) and washed with water (2 × 20 ml) and brine (10 ml). The organic phase was collected, dried ($MgSO_4$), filtered and the solvent evaporated off to yield the phenyl allylic sulfoxide (**22**), which was not purified further. To a solution of the crude allylic sulfoxide (**22**) in anhydrous methanol (10–20 ml) was added trimethyl phosphite (2.0 eq), under an atmosphere of dry nitrogen, and the whole was heated under reflux for a total of 10–15 hours. Upon completion of the reaction (TLC), the solvent was removed *in vacuo* and the crude product was purified by flash silica column chromatography (eluent: PE:EtOAc/5:2) to yield the *(o-aminobenzenesulfonamidyl)alkenols* (**18**) as yellow oils which darkened on standing at room temperature, but which were stored without detriment at −15 °C and used after 24 hours in the next step. Data for samples of compounds (**18a–c**) were as follows:

4-(o-Aminobenzenesulfonamidyl)-but-1-en-3-ol (**18a**) was obtained as a yellow oil (0.6120 g, 86% yield) from 2-(*o*-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (**21a**; 0.8000 g, 2.94 mmol).

δ_H (400 MHz, $CDCl_3$): 2.85 (1 H, ddd, *J* 13.1, 8.0, 5.2, C*H*$_2$NH), 3.08 (1 H, ddd, *J* 13.1, 7.6, 3.7, C*H*$_2$NH), 4.15–4.17 (1 H, m, C*H*OH), 4.75 (2H, s, br, N*H*$_2$), 5.17 (1 H, dt, *J* 10.5, 1.0, HC=C*H*$_2$), 5.28 (1 H, dt, *J* 17.2, 1.2, HC=C*H*$_2$), 5.44 (1 H, t, br, *J* 5.9, SO_2N*H*), 5.73 (1 H, ddd, *J* 17.1, 10.6, 5.7, H_2C=C*H*), 6.78–6.84 (2 H, m, 2 × Ar*H*), 7.34 (1 H, td, *J* 7.7, 1.5, Ar*H*), 7.71 (1 H, dd, *J* 8.0, 1.4, Ar*H*). δ_C (100 MHz, $CDCl_3$): 48.2 (*C*H$_2$), 71.1 (*C*H), 117.0 (*C*H$_2$), 117.8 (*C*H), 117.9 (*C*H), 121.5 (q), 129.6 (*C*H), 134.3 (*C*H), 137.0 (*C*H), 145.0 (q). υ_{max} (cm^{-1}): 3476 (bm), 3377 (bm), 2987 (m), 2928 (m), 1620 (m), 1600 (m), 1573 (w), 1483 (s), 1456 (s), 1332 (s), 1156 (s), 1073 (m), 896 (m), 747 (s). EI+ mass spectrum (m/z, %): 242 ($[M]^+$, 5%), 224 ($[M–H_2O]^+$, 5%), 185 (35%), 168 (15%), 156 (50%), 108 (35%), 92 (100%), 65 (98%), 57 (90%). CI+ mass spectrum (m/z, %): 260 ($[M+NH_4]^+$, 95%), 243 ($[M+H]^+$, 100%). HRMS (ESI+): found $[M+H]^+$ 243.0804, $C_{10}H_{14}N_2O_3S$ requires 243.0803.

4-(o-Aminobenzenesulfonamidyl)-2-methyl-but-1-en-3-ol (**18b**) was obtained as a yellow oil (1.115 g, 89% yield) from 2-(*o*-aminobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (**21b**; 1.400 g, 4.89 mmol).

δ_H (400 MHz, $CDCl_3$): 1.66 (3 H, s, C*H*$_3$), 2.88 (1 H, ddd, *J* 12.9, 8.0, 3.5, C*H*$_2$NH), 3.15 (1 H, ddd, *J* 13.1, 8.0, 3.6, C*H*$_2$NH), 4.06 (1 H, dd, *J* 7.8, 3.6, C*H*OH), 4.88 (2H, s, br, N*H*$_2$), 4.93 (1 H, bs, MeC=C*H*$_2$), 5.00 (1 H, d, *J* 0.9, MeC=C*H*$_2$), 5.11 (1 H, s, br, SO_2N*H*), 6.80

(1 H, d, *J* 8.2, Ar*H*), 6.85 (1 H, td, *J* 7.7, 1.0, Ar*H*), 6.85 (1 H, dd, *J* 7.7, 1.0, Ar*H*), 7.36 (1 H, td, *J* 7.7, 1.7, Ar*H*), 7.74 (1 H, dd, *J* 8.0, 1.5, Ar*H*). δ_C (100 MHz, $CDCl_3$): 18.3 (*C*H_3), 47.0 (*C*H_2), 73.4 (*C*H), 112.4 (*C*H_2), 117.8 (*C*H), 118.1 (*C*H), 121.7 (q), 129.7 (*C*H), 134.3 (*C*H), 144.1 (q), 145.0 (q). υ_{max} (cm^{-1}): 3477 (bm), 3378 (bm), 2986 (m), 2926 (m), 1619 (m), 1600 (m), 1573 (w), 1483 (s), 1456 (s), 1331 (m), 1155 (s), 1090 (m), 910 (m), 756 (s). EI+ mass spectrum (m/z, %): 256 ($[M]^+$, 3%), 238 ($[M–H_2O]^+$, 4%), 185 (30%), 168 (15%), 156 (50%), 108 (35%), 92 (100%), 71 (35%), 65 (90%). CI+ mass spectrum (m/z, %): 274 ($[M+NH_4]^+$, 100%), 257 ($[M+H]^+$, 90%). HRMS (ESI+): found $[M+H]^+$ 257.0956, $C_{11}H_{16}N_2O_3S$ requires 257.0960.

(E)-5-(o-Aminobenzenesulfonamidyl)-hex-2-en-4-ol (**18c**) was obtained as a yellow oil (0.8900 g, 82% yield) from 2-(*o*-aminobenzenesulfonyl)-3,6-dihydro-3,6-dimethyl-1,2-thiazine 1-oxide (**21c**; 1.200 g, 4.00 mmol).

δ_H (400 MHz, $CDCl_3$): 1.02 (3 H, d, *J* 6.7, C*H*$_3$CHNH), 1.62 (3 H, dd, *J* 6.5, 1.3, C*H*$_3$CH=CH), 3.13–3.18 (1 H, m, C*H*Me), 3.80 (1 H, t, *J* 6.6, C*H*OH), 3.99 (2H, s, br, N*H*$_2$), 5.22 (1 H, d, br, *J* 8.1, SO_2N*H*), 5.31 (1 H, ddd, *J* 15.3, 7.5, 1.6, MeHC=C*H*), 5.67 (1 H, dq, *J* 15.3, 6.6, CH=C*H*Me), 6.78 (1 H, d, *J* 8.0, Ar*H*), 6.80 (1 H, t, *J* 7.5, Ar*H*), 7.32 (1 H, td, *J* 7.7, 1.5, Ar*H*), 7.72 (1 H, dd, *J* 8.0, 1.4, Ar*H*). δ_C (100 MHz, $CDCl_3$): 17.7 (*C*H_3), 17.8 (*C*H_3), 54.2 (*C*H), 75.7 (*C*H), 117.7 (*C*H), 117.8 (*C*H), 122.3 (q), 129.5 (*C*H), 129.7 (*C*H), 130.0 (*C*H), 134.0 (*C*H), 144.9 (q). υ_{max} (cm^{-1}): 3474 (bm), 3374 (bm), 2975 (m), 2931 (m), 1621 (m), 1600 (m), 1568 (w), 1483 (s), 1455 (m), 1318 (s), 1155 (s), 1080 (m), 968 (m), 755 (s). EI+ mass spectrum (m/z, %): 270 ($[M]^+$, 1%), 252 ($[M–H_2O]^+$, 6%), 199 (25%), 182 (20%), 172 (25%), 156 (30%), 108 (35%), 92 (98%), 71 (10%), 65 (100%). CI+ mass spectrum (m/z, %): 288 ($[M+NH_4]^+$, 20%), 271 ($[M+H]^+$, 25%). HRMS (ESI+): found $[M+H]^+$ 271.1116, $C_{12}H_{18}N_2O_3S$ requires 271.1116.

4.4 *Synthesis of {o-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl} alkenones (24)*

4.4.1 Stage 1. Synthesis of the {o-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl} alkenols. To a solution of the *o*-(aminobenzenesulfonamidyl)alkenol (**18**; ~0.8–1.6 mmol, 1.0 eq) in anhydrous dichloromethane (10 ml) was added solid sodium hydrogen carbonate (2.1 eq) and 9-fluorenylmethyl chloroformate (2.1 eq) and the reaction mixture was left stirring at room temperature under nitrogen for a total of 6–8 hours, whilst being monitored by TLC. Upon completion of the reaction, the solvent was removed *in vacuo* and the crude product was purified by column chromatography (eluent: PE:EtOAc/3:1) to yield the desired *{o-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl} alkenols*, as follows:

4-{o-[(9'-Fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl}-but-1-en-3-ol was obtained as a colourless solid (0.3085 g, 81% yield) from 4-(*o*-aminobenzenesulfonamidyl)-but-1-en-3-ol (**18a**; 0.2000 g, 0.82 mmol), mp 204–205 °C.

δ_H (400 MHz, $CDCl_3$): 2.90 (1 H, ddd, *J* 12.8, 8.0, 4.7, C*H*$_2$NH), 3.15 (1 H, ddd, *J* 11.7, 8.0, 3.7, C*H*$_2$NH), 3.57 (1 H, s, br, O*H*), 4.05–4.12 (1 H, m, C*H*OH), 4.33 (1 H, t, *J* 7.1, C*H*C*H*$_2$OCONH), 4.52 (2H, d, *J* 7.2, CHC*H*$_2$OCONH), 5.02 (1 H, q, *J* 5.7, SO_2N*H*), 5.18 (1 H, d, *J* 10.5, HC=C*H*$_2$), 5.25 (1 H, d, *J* 17.3, HC=C*H*$_2$), 5.71 (1 H, ddd, *J* 17.1, 10.8, 5.7, H_2C=C*H*), 7.22 (1 H, t, *J* 7.7, Ar*H*), 7.36 (2H, t, *J* 7.5, 2 × Ar*H*), 7.45 (2H, t, *J* 7.5, 2 × Ar*H*), 7.59 (1 H, t, *J* 7.8, Ar*H*), 7.65 (2H, d, *J* 7.4, 2 × Ar*H*), 7.81 (2H, d, *J* 7.5, 2 × Ar*H*), 7.90 (1 H, dd, *J* 8.0, 1.0, Ar*H*), 8.15 (1 H, d, br, *J* 7.8, Ar*H*), 8.69 (1 H, s, br, CO_2N*H*). δ_C (100 MHz, $CDCl_3$): 46.9 (*C*H), 47.9 (*C*H_2), 67.7 (*C*H_2), 70.9 (*C*H), 111.3 (*C*H_2), 117.5 (q), 118.0 (q), 120.1 (*C*H), 122.3 (*C*H), 123.5 (*C*H), 125.1 (*C*H), 127.2 (*C*H), 127.9 (*C*H), 129.4 (*C*H), 134.3 (*C*H), 136.8 (*C*H), 141.4 (q), 143.6 (q), 153.3 (q, *C*O_2NH).

υ_{max} (cm^{-1}): 3512 (bw), 3355 (bm), 2925 (m), 2853 (m), 1735 (s), 1588 (s), 1530 (s), 1469 (m), 1458 (s), 1329 (s), 1291 (m), 1250 (m), 1154 (s), 1132 (m), 1082 (m), 1047 (m), 933 (w), 757 (s), 668 (m). ESI+ mass spectrum (m/z, %): 487 ($[M+Na]^+$, 55%), 465 ($[M]^+$, 20%). HRMS (CI+): found $[M+NH_4]^+$ 482.1747, $C_{25}H_{24}N_2O_5S$ requires 482.1750. C, H, N(%): found C 64.4, H 5.1, N 5.9; $C_{25}H_{24}N_2O_5S$ requires C 64.6, H 5.2, N 6.0.

4-{o-[(9'-Fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl}-2-methyl-but-1-en-3-ol was obtained as a colourless solid (0.5675 g, 76% yield) from 4-(*o*-aminobenzenesulfonamidyl)-2-methyl-but-1-en-3-ol (**18b**; 0.4000 g, 1.56 mmol), mp 198–200 °C.

δ_H (400 MHz, $CDCl_3$): 1.60 (3 H, s, C*H*$_3$), 1.94 (1 H, d, *J* 3.7, O*H*), 2.93 (1 H, ddd, *J* 12.7, 8.4, 4.1, C*H*$_2$NH), 3.18 (1 H, ddd, *J* 12.3, 8.2, 4.1, C*H*$_2$NH), 3.95 (1 H, ddd, *J* 12.5, 11.9, 3.9, C*H*OH), 4.32 (1 H, t, *J* 7.1, C*H*CH$_2$OCONH), 4.52 (2H, d, *J* 7.2, CHC*H*$_2$OCONH), 4.88 (1 H, s, HC=C*H*$_2$), 4.93 (1 H, s, HC=C*H*$_2$), 5.07 (1 H, dd, *J* 8.1, 3.9, SO_2N*H*), 7.21 (1 H, t, *J* 7.8, Ar*H*), 7.36 (2H, t, *J* 7.4, 2 × Ar*H*), 7.44 (2H, t, *J* 7.4, 2 × Ar*H*), 7.58 (1 H, t, *J* 7.2, Ar*H*), 7.65 (2H, d, *J* 7.4, 2 × Ar*H*), 7.81 (2H, d, *J* 7.5, 2 × Ar*H*), 7.91 (1 H, dd, *J* 8.0, 1.4, Ar*H*), 8.15 (1 H, d, br, *J* 8.0, Ar*H*), 8.72 (1 H, s, br, CO_2N*H*). δ_C (100 MHz, $CDCl_3$): 18.2 (*C*H$_3$), 46.7 (*C*H$_2$), 46.9 (*C*H), 67.7 (*C*H$_2$), 73.2 (*C*H), 112.6 (*C*H$_2$), 120.1 (*C*H), 122.2 (*C*H), 122.8 (q), 123.4 (*C*H), 125.1 (*C*H), 127.2 (*C*H), 127.9 (*C*H), 129.3 (*C*H), 134.3 (*C*H), 136.1 (q), 141.3 (q), 143.6 (q), 143.9 (q), 153.3 (q, *C*O_2NH). υ_{max} (cm^{-1}): 3515 (bw), 3354 (bm), 2924 (m), 2851 (m), 1737 (s), 1588 (s), 1530 (s), 1470 (m), 1444 (s), 1328 (s), 1291 (m), 1249 (m), 1153 (s), 1133 (m), 1083 (m), 1049 (m), 910 (w), 757 (s), 668 (m). ESI+ mass spectrum (m/z, %): 979 ($[2M+Na]^+$, 5%), 957 ($[2M]^+$, 15%), 501 ($[M+Na]^+$, 20%), 479 ($[M]^+$, 70%). C, H, N(%): found C 65.5, H 5.4, N 5.9; $C_{26}H_{26}N_2O_5S$ requires C 65.2, H 5.5, N 5.9.

(E)-5-{o-[(9'-Fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl}-hex-2-en-4-ol was obtained as a colourless solid (0.3930 g, 72% yield) from (*E*)-5-(*o*-aminobenzenesulfonamidyl)-hex-2-en-4-ol (**18c**; 0.3000 g, 1.11 mmol, 1.0 eq), mp 186–187 °C.

δ_H (400 MHz, $CDCl_3$): 1.09 (3 H, d, *J* 6.7, C*H*$_3$CHNH), 1.59 (3 H, dd, *J* 6.5, 1.5, C*H*$_3$CH=CH), 1.88 (1 H, s, br, O*H*), 3.21 (1 H, q, *J* 6.0, MeC*H*NH), 3.80 (1 H, t, *J* 6.2, C*H*OH), 4.32 (1 H, t, *J* 6.7, C*H*CH$_2$OCONH), 4.51 (2H, d, *J* 7.2, CHC*H*$_2$OCONH), 5.12 (1 H, d, br, *J* 7.6, SO_2N*H*), 5.24 (1 H, ddd, *J* 15.3, 7.5, 1.6, MeHC=C*H*), 5.64 (1 H, dq, *J* 15.3, 6.6, HC=C*H*Me), 7.18 (1 H, t, *J* 7.1, Ar*H*), 7.36 (2H, t, *J* 7.5, 2 × Ar*H*), 7.44 (2H, t, *J* 7.4, 2 × Ar*H*), 7.55 (1 H, t, *J* 7.0, Ar*H*), 7.64 (2H, t, *J* 6.8, 2 × Ar*H*), 7.80 (2H, d, *J* 7.5, 2 × Ar*H*), 7.91 (1 H, dd, *J* 8.0, 1.5, Ar*H*), 8.16 (1 H, d, br, *J* 7.5, Ar*H*), 8.79 (1 H, s, br, CO_2N*H*). δ_C (100 MHz, $CDCl_3$): 17.7 (*C*H$_3$), 18.1 (*C*H$_3$), 46.9 (*C*H), 54.2 (*C*H), 67.6 (*C*H$_2$), 75.3 (*C*H), 120.1 (*C*H), 121.8 (*C*H), 123.2 (*C*H), 125.0 (*C*H), 127.2 (*C*H), 127.8 (*C*H), 129.3 (*C*H), 129.5 (*C*H), 130.4 (*C*H), 134.0 (*C*H), 136.0 (q), 141.3 (q), 143.6 (q), 153.2 (q, *C*O_2NH). υ_{max} (cm^{-1}): 3512 (bw), 3354 (bm), 2923 (m), 2850 (m), 1736 (s), 1589 (s), 1530 (s), 1470 (m), 1444 (s), 1329 (s), 1291 (s), 1247 (m), 1155 (s), 1133 (m), 1081 (m), 1049 (m), 967 (m), 758 (s), 668 (m). ESI+ mass spectrum (m/z, %): 515 ($[M+Na]^+$, 100%). C, H, N (%): found C 65.7, H 5.7, N 5.8; $C_{27}H_{28}N_2O_5S$ requires C 65.8, H 5.7, N 5.7.

4.4.2 Stage 2. Formation of {o-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl} alkenones (24) by oxidation of the {o-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl} alkenols. To a solution of Dess-Martin periodinane (1.1 eq) in anhydrous dichloromethane (10 ml) was added a solution of the *o*-[*N*-(9-fluorenylmethoxycarbonyl)aminobenzenesulfonamidyl] alkenol from Stage 1 in anhydrous dichloromethane (5 ml) at room temperature and the reaction mixture was stirred for 1 hour, whilst being monitored by TLC. Upon completion of the reaction the solvent was evaporated off and the crude product was purified by flash column chromatography (eluent: PE:EtOAc/3:1)

to yield the *{o-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl} alkenones* (**24**), as follows:

4-{o-[(9'-Fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl}-but-1-en-3-one (**24a**) was obtained as a slightly unstable (noticeable degradation after two days at room temperature) pale yellow oil (0.0477 g, 78% yield) from 4-{*o*-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl}-but-1-en-3-ol (0.0600 g, 0.13 mmol).

δ_H (400 MHz, $CDCl_3$): 4.05 (2H, d, *J* 4.7, CH_2NH), 4.36 (1 H, t, *J* 7.3, C*H*CH_2OCONH), 4.52 (2H, d, *J* 7.4, CHCH_2OCONH), 5.73 (1 H, t, br, *J* 4.5, SO_2N*H*), 5.93 (1 H, dd, *J* 9.8, 1.5, H_2C=C*H*), 6.21–6.34 (2H, m, HC=CH_2), 7.19 (1 H, t, *J* 7.6, Ar*H*), 7.37 (2H, t, *J* 7.4, 2 × Ar*H*), 7.45 (2H, t, *J* 7.4, 2 × Ar*H*), 7.58 (1 H, t, *J* 7.8, Ar*H*), 7.77 (2H, d, *J* 7.4, 2 × Ar*H*), 7.81 (2H, d, *J* 7.5, 2 × Ar*H*), 7.89 (1 H, dd, *J* 8.0, 1.3, Ar*H*), 8.23 (1 H, d, br, *J* 8.1, Ar*H*), 8.82 (1 H, s, br, CO_2N*H*). δ_C (100 MHz, $CDCl_3$): 46.9 (*C*H), 49.2 (*C*H_2), 67.7 (*C*H_2), 120.0 (*C*H), 121.9 (*C*H), 123.1 (*C*H), 125.1 (*C*H), 125.9 (q), 127.2 (*C*H), 127.8 (*C*H), 129.2 (*C*H), 130.8 (*C*H_2), 132.7 (*C*H), 134.5 (*C*H), 136.4 (q), 141.3 (q), 143.6 (q), 153.1 (q, *C*O_2NH), 192.1 (q, *C*=O). υ_{max} (cm^{-1}): 3355 (bm), 2920 (s), 2850 (s), 1735 (s), 1589 (s), 1529 (s), 1470 (m), 1459 (s), 1330 (s), 1291 (m), 1240 (m), 1155 (s), 1133 (m), 1079 (m), 1048 (m), 756 (s), 667 (m). ESI+ mass spectrum (m/z, %): 485 ($[M+Na]^+$, 40%); CI mass spectrum (m/z, %): 480 ($[M+NH_4]^+$, 50%).

4-{ o-[(9'-Fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl }-2-methyl-but-1-en-3-one (**24b**) was obtained as a pale yellow oil which solidified on standing (0.1700 g, 85% yield) from 4-{*o*-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl}-2-methyl-but-1-en-3-ol (0.2000 g, 0.42 mmol), mp 176–178 °C.

δ_H (400 MHz, $CDCl_3$): 1.84 (3 H, s, CH_3), 4.18 (2H, d, *J* 4.6, CH_2NH), 4.36 (1 H, t, *J* 7.3, C*H*CH_2OCONH), 4.51 (2H, d, *J* 7.4, CHCH_2OCONH), 5.70 (1 H, t, *J* 4.4, SO_2N*H*), 5.84 (2H, dd, *J* 5.0, 1.5, MeC=CH_2), 7.19 (1 H, td, *J* 8.0, 0.8, Ar*H*), 7.37 (2H, td, *J* 7.6, 0.9, 2 × Ar*H*), 7.45 (2H, t, *J* 7.3, 2 × Ar*H*), 7.58 (1 H, td, *J* 8.4, 1.2, Ar*H*), 7.68 (2H, d, *J* 7.4, 2 × Ar*H*), 7.81 (2H, d, *J* 7.5, 2 × Ar*H*), 8.00 (1 H, dd, *J* 7.8, 1.6, Ar*H*), 8.24 (1 H, d, br, *J* 8.2, Ar*H*), 8.86 (1 H, s, br, CO_2N*H*). δ_C (100 MHz, $CDCl_3$): 17.2 (*C*H_3), 46.9 (*C*H), 47.5 (*C*H_2), 67.8 (*C*H_2), 120.0 (*C*H), 121.8 (*C*H), 123.1 (*C*H), 125.1 (*C*H), 126.0 (*C*H_2), 126.3 (q), 127.2 (*C*H), 127.8 (*C*H), 129.2 (*C*H), 134.4 (*C*H), 136.4 (q), 141.3 (q), 141.7 (q), 143.6 (q), 153.1 (q, *C*O_2NH), 193.3 (q, *C*=O). υ_{max} (cm^{-1}): 3349 (bm), 2924 (s), 2851 (s), 1733 (bs), 1587 (s), 1530 (s), 1470 (m), 1444 (s), 1330 (s), 1291 (m), 1236 (m), 1154 (s), 1133 (m), 1083 (m), 1048 (m), 757 (s), 668 (m). ESI+ mass spectrum (m/z, %): 499 ($[M+Na]^+$, 65%), 478 ($[M+H]^+$, 6%). C, H, N (%): found C 65.7, H 5.0, N 6.0; $C_{26}H_{24}N_2O_5S$ requires C 65.5, H 5.1, N 5.9.

(E)-5-{ o-[(9'-Fluorenylmethoxycarbonyl) amino]benzenesulfonamidyl }-hex-2-en-4-one (**24c**) was obtained as a pale yellow oil which solidified on standing (0.2650 g, 76% yield) from (*E*)-5-{*o*-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl}-hex-2-en-4-ol (0.3500 g, 0.71 mmol), mp 173–176 °C.

δ_H (400 MHz, $CDCl_3$): 1.31 (3 H, d, *J* 7.2, CH_3CHNH), 1.86 (3 H, dd, *J* 6.9, 1.6, CH_3CH=CH), 4.17 (1 H, dq, *J* 7.4, 7.2, MeC*H*NH), 4.37 (1 H, t, *J* 7.4, C*H*CH_2OCONH), 4.47–4.58 (2 H, m, CHCH_2OCONH), 5.92 (1 H, d, *J* 7.1, SO_2N*H*), 6.04 (1 H, dq, *J* 14.1, 1.5, *H*C=CHMe), 6.90 (1 H, dq, *J* 13.7, 6.9, Me*H*C=CH), 7.16 (1 H, td, *J* 7.8, 1.0, Ar*H*), 7.37 (2 H, td, *J* 7.4, 1.1, 2 × Ar*H*), 7.45 (2 H, t, *J* 7.4, 2 × Ar*H*), 7.55 (1 H, td, *J* 7.9, 1.4, Ar*H*), 7.69 (2H, t, *J* 7.4, 2 × Ar*H*), 7.81 (2H, d, *J* 7.5, 2 × Ar*H*), 7.86 (1 H, dd, *J* 8.0, 1.5, Ar*H*), 8.22 (1 H, d, br, *J* 8.1, Ar*H*), 8.81 (1 H, s, br, CO_2N*H*). δ_C (100 MHz, $CDCl_3$): 18.5 (*C*H_3), 19.5 (*C*H_3), 46.9 (*C*H), 55.2 (*C*H), 67.7 (*C*H_2), 120.0 (*C*H), 121.7 (*C*H), 123.0 (*C*H), 125.1 (*C*H), 126.7 (*C*H), 127.2 (*C*H), 127.8 (*C*H), 129.1 (*C*H), 134.3 (*C*H), 136.4 (q), 141.3 (q), 141.7 (q), 143.5 (q), 146.4 (*C*H), 153.0 (q, *C*O_2NH), 195.5 (q, *C*=O). υ_{max} (cm^{-1}): 3347 (bm), 2929 (m), 2851 (m), 1740 (s), 1587 (s), 1530 (s), 1470 (m), 1442 (s), 1332 (s), 1291

(s), 1240 (s), 1154 (s), 1132 (m), 1079 (s), 1048 (s), 759 (s), 668 (m). ESI+ mass spectrum (m/z, %): 1003 ([2M+Na]$^+$, 15%), 513 ([M+Na]$^+$, 100%), 491 ([M+H]$^+$, 15%). C, H, N (%): found C 66.4, H 5.4, N 5.8; $C_{27}H_{26}N_2O_5S$ requires C 66.1, H 5.4, N 5.7.

4.5 *Synthesis of 2,3-dihydro-3-hydroxy-1,2,5-benzothiadiazepine 1,1-dioxides (27)*

A solution of the {*o*-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl}alkenone (**24**; ~0.4–0.5 mmol) in a mixture of triethylamine and anhydrous dichloromethane (1:1 *V/V*, 10 ml) was heated at reflux under an atmosphere of dry nitrogen whilst being monitored by TLC. Upon completion (approx. 15 hours) of the reaction, the solvent was evaporated off and the crude residue was purified by flash silica column chromatography (eluent: PE:EtOAc/1:1) to yield the 1,2,5-benzothiadiazepine 1,1-dioxides (**27**) as follows:

4-Ethyl-2,3-dihydro-3-hydroxy-1,2,5-benzothiadiazepine 1,1-dioxide (**27a**) was obtained as a light yellow oil which solidified on standing (0.0716 g, 69% yield) from 4-{*o*-[(9'-fluorenylmethoxycarbonyl) amino]benzenesulfonamidyl]}-but-1-en-3-one (**24a**; 0.2000 g, 0.43 mmol), mp: 89–92 °C.

δ_H (400 MHz, $CDCl_3$): 1.06 (3 H, t, *J* 7.4, CH_3), 1.87 (1 H, dq, *J* 7.4, 3.8, MeCH_2), 2.08 (1 H, m, MeCH_2), 3.6–3.8 (1 H, bs, O*H*), 4.49 (1 H, d, *J* 3.8, C*H*OH), 7.12 (1 H, d, *J* 8.2, Ar*H*), 7.45 (1 H, t, *J* 7.7, Ar*H*), 7.57 (1 H, t, *J* 7.7, Ar*H*), 7.96 (1 H, d, *J* 8.0, Ar*H*). δ_C (100 MHz, $CDCl_3$): 9.1 (*C*H_3), 28.5 (*C*H_2), 72.3 (*C*HOH), 117.0 (*C*H), 121.6 (q), 124.7 (*C*H), 127.2 (*C*H), 132.9 (*C*H), 133.6 (q), 160.4 (q). υ_{max} (cm^{-1}): 3475 (bm), 3277 (bm), 2963 (m), 2927 (m), 1604 (m), 1560 (w), 1525 (m), 1481 (m), 1440 (w), 1297 (m), 1261 (s), 1158 (s), 1079 (s), 1020 (s), 801 (s), 759 (s). ESI+ mass spectrum (m/z, %): 743 ([3M+Na]$^+$, 5%), 503 ([2M+Na]$^+$, 30%), 481 ([2M+H]$^+$, 6%), 263 ([M+Na]$^+$, 70%), 241 ([M+H]$^+$, 100%). HRMS (ESI+): found [M+H]$^+$ 241.0642, $C_{10}H_{12}N_2O_3S$ requires 241.0647. C, H, N(%): found C 49.9, H 5.1, N 11.9; $C_{10}H_{12}N_2O_3S$ requires C 50.0, H 5.0, N 11.7.

2,3-Dihydro-3-hydroxy-4-(i-propyl)-1,2,5-benzothiadiazepine 1,1-dioxide (**27b**) was similarly obtained as a yellow solid (0.0830 g, 62% yield), mp: 117–119 °C from 4-{*o*-[(9'-fluorenylmethoxycarbonyl) aminobenzenesulfonamidyl}-but-1-en-3-one (**24b**; 0.2500 g, 0.53 mmol).

δ_H (400 MHz, $CDCl_3$): 0.87 (3 H, d, *J* 6.9, CH_3), 1.07 (3 H, d, *J* 6.9, CH_3), 2.34 (1 H, qq, *J* 6.8, 6.7, Me_2C*H*), 3.4–3.5 (1 H, bs, O*H*), 4.33 (1 H, d, *J* 3.3, C*H*OH), 7.13 (1 H, d, *J* 8.2, Ar*H*), 7.43 (1 H, t, *J* 7.6, Ar*H*), 7.54 (1 H, t, *J* 7.8, Ar*H*), 7.92 (1 H, d, *J* 7.9, Ar*H*), 9.40 (1 H, s, br, SO_2N*H*). δ_C (100 MHz, $CDCl_3$): 15.3 (*C*H_3), 19.0 (*C*H_3), 32.8 (*C*H), 75.1 (*C*H), 117.2 (*C*H), 121.6 (q), 124.5 (*C*H), 127.1 (*C*H), 133.0 (*C*H), 133.6 (q), 160.8 (q). υ_{max} (cm^{-1}): 3477 (bm), 3261 (bm), 2965 (m), 2930 (m), 1602 (m), 1560 (w), 1523 (m), 1482 (m), 1442 (w), 1297 (s), 1260 (s), 1161 (s), 1082 (s), 1028 (s), 800 (s), 756 (m). EI+ mass spectrum (m/z, %): 254 ([M]$^+$, 2%), 237 ([M–OH]$^+$, 4%), 212 ([(M-CHMe$_2$)+H]$^+$, 25%), 196 (20%), 147 (70%), 119 (50%), 108 (15%), 91 (45%), 77 (15%), 64 (25%). ESI+ mass spectrum (m/z, %): 785 ([3M+Na]$^+$, 4%), 763 ([3M+H]$^+$, 2%), 531 ([2M+Na]$^+$, 35%), 509 ([2M+H]$^+$, 10%), 277 ([M+Na]$^+$, 35%), 255 ([M+H]$^+$, 100%). HRMS (ESI+): found [M+H]$^+$ 255.0803, $C_{11}H_{14}N_2O_3S$ requires 255.0803. C, H, N (%): found C 51.8, H 5.6, N 10.8; $C_{11}H_{14}N_2O_3S$ requires C 52.0, H 5.5, N 11.0.

2,3-Dihydro-3-hydroxy-3-methyl-4-propyl-1,2,5-benzothiadiazepine 1,1-dioxide (**27c**) was obtained as a yellow solid (0.0621 g, 57%), mp: 107–111 °C from *(E)-5-{o-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl}-hex-2-en-4-one* (**24c**, 0.2000 g, 0.41 mmol).

δ_H (400 MHz, $CDCl_3$): 1.32 (3 H, t, *J* 10.2, CH_3), 1.63 (2H, m, CH_2CH_2Me), 1.80 (1 H, m, CH_2CH_2Me), 2.02 (3 H, s, CH_3), 2.08 (1 H, dt, *J* 10.4, 7.8, CH_2CH_2Me), 3.2–3.4 (1 H,

bs, O*H*), 4.83 (1 H, bs, C*H*OH), 6.87 (1 H, dt, *J* 14.8, 6.9, Ar*H*), 7.11 (1 H, s, br, SO_2NH), 7.35 (1 H, dt, *J* 7.9, 1.4, Ar*H*), 7.55 (1 H, dd, *J* 5.6, 2.2, Ar*H*), 7.73 (1 H, dd, 5.6, 2.2, Ar*H*), 7.79 (1 H, dd, *J* 8.0, 1.2, Ar*H*). δ_C (100 MHz, $CDCl_3$): 14.0 (CH_3), 23.7 (CH_3), 28.1 (CH_2), 31.7 (CH_2), 79.0 (q, *C*(OH)Me), 128.4 (*C*H), 128.8 (q), 128.8 (*C*H), 130.9 (*C*H), 134.2 (*C*H), 144.6 (q), 167.8 (q). υ_{max} (cm^{-1}, chloroform): 3377 (bs), 3100 (bs), 2965 (m), 1624 (m), 1482 (w), 1314 (w), 1482 (m), 1154 (m), 1107 (m), 1088 (w). EI+ mass spectrum (m/z, %): 268 ($[M]^+$, 2%), 253 ($[M\text{-}CH_3]^+$, 10%), 250 ($[M–H_2O]^+$, 14%), 217 (25%), 169 (100%), 154 (70%), 108 (15%), 91 (45%), 77 (15%), 64 (25%). ESI+ mass spectrum (m/z, %): 269 ($[M+H]^+$, 100%), 291 ($[M+Na]^+$, 20%), 537 ($[2M+H]^+$, 10%). HRMS (ESI+): found $[M+H]^+$ 269.0960, $C_{12}H_{16}N_2O_3S$ requires $[M+H^+]$ 269.0960. C, H, N (%): found C 54.0, H 5.8, N 10.4; $C_{12}H_{16}N_2O_3S$ requires C 53.7, H 6.0, N 10.4.

4.6 *Synthesis of (o-nitrobenzenesulfonamidyl)alkenols (37)*

4.6.1 Method 1. Synthesis of compounds (37a/b/c) from o-nitrobenzenesulfonamide (‘*in situ*’ method). To a solution of *o*-nitrobenzenesulfonamide (∼5–10 mmol, 1.0 eq) and anhydrous pyridine (2.0 eq) in anhydrous tetrahydrofuran (15 ml), under an atmosphere of dry nitrogen, was added, dropwise with stirring over a period of 3 hours, a solution of thionyl chloride (1.0 eq) in anhydrous tetrahydrofuran (5 ml), to yield the crude *N*-sulfinyl compound (**33**). Stirring of the crude reaction mixture was continued for a further 30 minutes, followed by dropwise addition of the appropriate 1,3-diene (isoprene and hexadiene used 1.6 eq at room temperature; butadiene used 10 eq at −20 °C), and the whole was left stirring at room temperature for 12–16 hours (isoprene and hexadiene) or at −20 °C for 6–8 hours (butadiene), whilst being monitored by TLC. Upon completion of the reaction, stirring was ceased and, under an atmosphere of dry nitrogen, the supernatant solution was transferred into a second dry flask via a syringe leaving the unwanted pyridinium hydrochloride precipitate behind, which was washed with anhydrous tetrahydrofuran (5 × 10 ml) and the washings transferred to the second flask. To the crude adduct solution was added, with stirring, a solution of phenylmagnesium bromide (3M in ether, 2.0 eq) at −78 °C under an atmosphere of dry nitrogen. The reaction mixture was kept at low temperature (<−40 °C) for 3–4 hours, whilst being monitored by TLC. Upon completion of the reaction, the mixture was quenched at −20 °C with saturated ammonium chloride solution (15 ml) and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (4 × 50 ml) and the combined extracts washed with water (2 × 10 ml) and brine (10 ml). The organic phase was collected, dried ($MgSO_4$), filtered and the solvent evaporated off to yield the crude phenyl allylic sulfoxide which was not purified further. To a solution of the crude allylic sulfoxide in anhydrous methanol (10 ml) was added trimethyl phosphite (2.0 eq), under an atmosphere of dry nitrogen, and the whole was heated under reflux for a total of 10–15 hours. Upon completion of the reaction (TLC), the solvent was removed *in vacuo* and the crude product was purified by flash silica column chromatography (eluent: PE:EtOAc/5:2) to yield the *(o-nitrobenzenesulfonamidyl)alkenols* (**37**) as follows:

4-(o-Nitrobenzenesulfonamidyl)-but-1-en-3-ol (**37a**) was obtained as a light yellow solid (1.0230 g, 38% yield) over the four steps from *o*-nitrobenzenesulfonamide (2.000 g, 9.90 mmol); mp 189–191 °C.

δ_H (400 MHz, $CDCl_3$): 3.08 (1 H, ddd, *J* 12.2, 7.3, 4.7, CH_2NH), 3.31 (1 H, ddd, *J* 12.4, 7.1, 4.6, CH_2NH), 4.33 (1 H, m, C*H*OH), 5.11 (1 H, d, *J* 10.5, HC=CH_2), 5.19 (1 H, d, *J* 14.8, HC=CH_2), 5.74 (1 H, ddd, *J* 15.1, 10.7, 6.6, *H*C=CH_2), 5.97 (1 H, s, br, N*H*), 7.72–7.77 (2H, m, 2 × Ar*H*), 7.87 (1 H, dt, *J* 7.8, 1.2, Ar*H*), 8.08 (1 H, dd, *J* 8.2, 0.9, Ar*H*). δ_C (100 MHz, $CDCl_3$): 45.3 (CH_2), 69.7 (*C*HOH), 112.6 (CH_2), 118.1 (*C*H), 127.8 (*C*H), 129.0 (*C*H), 131.1 (*C*H), 134.8 (*C*H), 140.6 (q), 147.9 (q). υ_{max} (cm^{-1}): 3576 (bm), 3301 (bm),

3111 (m), 2928 (w), 1588 (m), 1547 (s), 1236 (m), 1166 (s), 1108 (m), 1086 (m), 1008 (m). ESI+ mass spectrum (m/z, %): 295 ($[M+Na]^+$, 14%), 273 ($[M+H]^+$, 34%). C, H, N (%): found C 44.4, H 4.6, N 10.2; $C_{10}H_{12}N_2O_5S$ requires C 44.1, H 4.4, N 10.3.

2-Methyl-4-(o-nitrobenzenesulfonamidyl)-but-1-en-3-ol (**37b**) was obtained as a yellow waxy solid (0.6330 g, 45% yield) over the four steps from *o*-nitrobenzenesulfonamide (1.000 g, 4.95 mmol).

δ_H (400 MHz, $CDCl_3$): 1.69 (3 H, s, C*H*$_3$), 2.40 (1 H, s, br, O*H*), 3.08 (1 H, ddd, *J* 12.6, 7.7, 4.7, C*H*$_2$NH), 3.27–3.38 (1 H, m, C*H*$_2$NH), 4.17–4.19 (1 H, m, C*H*OH), 4.91 (1 H, s, MeC=C*H*$_2$), 5.01 (1 H, s, MeC=C*H*$_2$), 5.78 (1 H, s, br, N*H*), 7.72–7.77 (2H, m, 2 × Ar*H*), 7.83–7.93 (1 H, m, Ar*H*), 8.11–8.15 (1 H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 18.3 (*C*H$_3$), 47.5 (*C*H$_2$), 73.4 (*C*HOH), 112.6 (*C*H$_2$), 125.4 (*C*H), 130.9 (*C*H), 132.8 (*C*H), 133.6 (*C*H), 140.1 (q), 143.9 (q), 147.9 (q). υ_{max} (cm^{-1}): 3550 (bm), 3333 (bm), 3096 (m), 2953 (m), 1594 (m), 1539 (s), 1441 (m), 1410 (m), 1343 (s), 1239 (m), 1166 (s), 1126 (m), 1090 (m), 1024 (m), 912 (m), 854 (m), 783 (m), 741 (m). ESI+ mass spectrum (m/z, %): 309 ($[M+Na]^+$, 45%), 287 ($[M+H]^+$, 4%). C, H, N (%): found C 46.4, H 4.8, N 9.8; $C_{11}H_{14}N_2O_5S$ requires C 46.1, H 4.9, N 9.8.

(E)-5-(o-Nitrobenzenesulfonamidyl)-hex-2-en-4-ol (**37c**) was obtained as a yellow solid (0.6490 g, 44% yield), mp: 163–166 °C, over the four steps from *o*-nitrobenzenesulfonamide (1.000 g, 4.95 mmol).

δ_H (400 MHz, $CDCl_3$): 1.14 (3 H, d, *J* 6.8, C*H*$_3$CH=CH), 1.55 (3 H, dd, *J* 6.4, 1.0, C*H*$_3$CHNH), 2.35 (1 H, s, br, O*H*), 3.42–3.51 (1 H, m, MeC*H*NH), 3.92 (1 H, dd, *J* 6.8, 5.3, C*H*OH), 5.31 (1 H, ddd, *J* 15.3, 7.3, 1.5, CH=C*H*Me), 5.67 (1 H, dq, *J* 15.4, 6.6, MeHC=C*H*), 5.70 (1 H, d, br, *J* 7.0, N*H*), 7.71–7.74 (2H, m, 2 × Ar*H*), 7.84–7.87 (1 H, m, Ar*H*), 8.12–8.14 (1 H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 17.6 (*C*H$_3$), 18.1 (*C*H$_3$), 54.8 (*C*H), 75.1 (*C*HOH), 125.2 (*C*H), 129.7 (*C*H), 129.9 (*C*H), 130.6 (*C*H), 132.8 (*C*H), 133.3 (*C*H), 134.7 (q), 147.6 (q). υ_{max} (cm^{-1}): 3550 (bm), 3365 (bm), 3097 (m), 2955 (m), 1671 (w), 1594 (w), 1541 (s), 1442 (m), 1410 (m), 1362 (s), 1241 (m), 1169 (s), 1125 (m), 1061 (m), 1025 (m), 968 (m), 854 (m), 784 (m), 743 (m). CI+ mass spectrum (m/z, %): 318 ($[M+NH_4]^+$, 100%), 300 ($[M]^+$, 45%). C, H, N (%): found C 48.3, H 5.2, N 9.3; $C_{12}H_{16}N_2O_5S$ requires C 48.0, H 5.4, N 9.3.

4.6.2 Method 2. (E)-5-(o-Nitrobenzenesulfonamidyl)-hex-2-en-4-ol (37c) from the thiazine 1-oxide (34c). Stage 1: Synthesis of 3,6-dihydro-3,6-dimethyl-2-(o-nitrobenzenesulfonyl)-1,2-thiazine 1-oxide (34c). To a solution of *o*-nitrobenzenesulfonamide (1.000 g, 4.95 mmol, 1.0 eq) in anhydrous benzene (15 ml) [CAUTION: SUSPECTED CARCINOGEN – see above for an alternative synthesis of compound **37c**] was added, under an atmosphere of dry nitrogen, thionyl chloride (0.54 ml, 7.42 mmol), and the whole was heated at reflux in an oil bath for 3 days (72 hours). The reaction mixture was allowed to cool to room temperature and the solvent and excess thionyl chloride were removed *in vacuo* to yield *N*-sulfinyl-*o*-nitrobenzenesulfonamide (**33**) as a brown oil. To the crude *N*-sulfinyl-*o*-nitrobenzenesulfonamide (**33**) in anhydrous tetrahydrofuran (15 ml) was added 2,4-hexadiene (0.90 ml, 7.91 mmol) and the reaction mixture was stirred at room temperature whilst being monitored by TLC. After completion of the reaction (16 hours) the solvent was removed *in vacuo* and the crude product was purified by flash silica chromatography (eluent: PE:EtOAc/2:1) to yield *3,6-dihydro-3,6-dimethyl-2-(o-nitrobenzenesulfonyl)-1,2-thiazine 1-oxide* (**34c**; 0.9830 g, 60% yield) as a pale yellow solid, mp: 110–112 °C.

δ_H (400 MHz, $CDCl_3$): 1.39 (3 H, d, *J* 7.4, C*H*$_3$CHS=O), 1.56 (3 H, d, *J* 7.0, C*H*$_3$CHN), 3.30–3.38 (1 H, m, MeC*H*S=O), 4.57 (1 H, ddq, *J* 11.1, 3.4, 1.8, MeC*H*N), 5.45 (1 H, ddd, *J* 11.0, 2.5, 2.0, HC=C*H*), 5.96 (1 H, ddd, *J* 11.0, 3.4, 2.9, HC=C*H*), 7.71–7.91 (3 H, m, 3 × Ar*H*), 8.19 (1 H, dd, *J* 8.3, 1.1, Ar*H*). δ_C (100 MHz, $CDCl_3$): 15.7 (*C*H$_3$), 23.5 (*C*H$_3$),

51.8 (*C*H), 53.1 (*C*H), 119.5 (*C*H), 124.8 (*C*H), 129.5 (*C*H), 131.3 (*C*H), 132.5 (*C*H), 133.0 (q), 134.8 (*C*H), 147.6 (q). υ_{max} (cm^{-1}): 3106 (w), 2934 (w), 1593 (w), 1545 (s), 1442 (m), 1371 (s), 1301 (w), 1173 (s), 1131 (m), 1108 (m), 1059 (m), 990 (w), 853 (m), 758 (s), 658 (m), 626 (m). EI+ mass spectrum (m/z, %): 331 ($[M+H]^+$, 2%), 282 ($[M–SO]^+$, 2%), 186 (20%), 144 (10%), 96 (10%), 82 (100%), 67 (85%), 64 (30%). CI+ mass spectrum (m/z, %): 348 ($[M+NH_4]^+$, 100%), 331 ($[M+H]^+$, 15%). HRMS (ESI+): found $[M+H]^+$ 331.0419, $C_{12}H_{14}N_2O_5S_2$ requires 331.0422. C, H, N(%): found C 43.7, H 4.3, N 8.6; $C_{12}H_{14}N_2O_5S_2$ requires C 43.6, H 4.3, N 8.5.

Stage 2. Synthesis of (E)-5-(o-nitrobenzenesulfonamidyl)-hex-2-en-4-ol (37c). A solution of phenylmagnesium bromide (3 M in ether, 2.0 eq) was added with stirring to a solution of 3,6-dihydro-3,6-dimethyl-2-(*o*-nitrobenzenesulfonyl)-1,2-thiazine 1-oxide (**34c**; 1.000 g, 3.03 mmol) in anhydrous tetrahydrofuran (10 ml) at −78 °C, under an atmosphere of dry nitrogen. The reaction mixture was kept at low temperature (<−40 °C) for 3–4 hours, whilst being monitored by TLC. Upon completion of the reaction, the mixture was quenched at −20 °C with saturated ammonium chloride solution (15 ml) and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (2 × 10 ml) and washed with water (2 × 10 ml) and brine (10 ml). The organic phase was collected, dried ($MgSO_4$), filtered and the solvent evaporated off to yield the intermediate phenyl allylic sulfoxide which was not purified further. To a solution of the crude allylic sulfoxide in anhydrous methanol (10 ml) was added trimethyl phosphite (2.0 eq), under an atmosphere of dry nitrogen, and the whole was heated at reflux temperature for a total of 12–15 hours. Upon completion of the reaction (TLC), the solvent was removed *in vacuo* and the crude product was purified by flash silica column chromatography (eluent: PE:EtOAc/5:2) to yield *(E)-5-(o-nitrobenzenesulfonamidyl)-hex-2-en-4-ol* (**37c**) as a yellow oil (0.8100 g, 89% yield), which solidified on standing and was identical in all aspects to that obtained in Method 1, above.

4.7 *Synthesis of (o-nitrobenzenesulfonamidyl)alkenones (38) by oxidation of alkenols (37)*

To a solution of Dess-Martin periodinane (1.1 eq) in dry dichloromethane (10 ml) was added a solution of the allylic alcohol (**37**; 1–2 mmol, 1.0 eq) in dry dichloromethane (5 ml) at room temperature and the reaction mixture was stirred for 1 hour, whilst being monitored by TLC. Once the reaction was complete, the solvent was evaporated off and the crude product was purified by flash silica column chromatography (eluent: PE:EtOAc/5:2) to yield the following products:

4-(o-Nitrobenzenesulfonamidyl)-but-1-en-3-one (**38a**) was obtained as an unstable (decomposes in less than one day at room temperature), partially characterised yellow oil (0.1980 g, 78% yield) from 4-(*o*-nitrobenzenesulfonyl)-but-1-en-3-ol (**37a**; 0.3500 g, 1.29 mmol).

δ_H (400 MHz, $CDCl_3$): 3.85 (2H, d, *J* 12.6, CH_2NH), 5.71 (1 H, dd, *J* 9.1, 2.3, HC=CH_2), 5.98 (1 H, dd, *J* 14.8, 2.5, HC=CH_2), 6.34 (1 H, dd, *J* 14.6, 9.3, *H*C=CH_2), 6.40 (1 H, s, br, N*H*), 7.78–7.82 (2 H, m, 2 × Ar*H*), 7.81 (1 H, dt, *J* 7.8, 1.2, Ar*H*), 8.10 (1 H, dd, *J* 8.1, 0.9, Ar*H*). δ_C (100 MHz, $CDCl_3$): 61.2 (CH_2), 117.4 (CH_2), 125.4 (*C*H), 130.9 (*C*H), 131.0 (*C*H), 132.8 (*C*H), 133.6 (*C*H), 136.8 (q), 146.3 (q), 185.1 (q, *C* = O). υ_{max} (cm^{-1}): 3462 (bm), 3330 (bm), 2945 (w), 1709 (s), 1598 (m), 1553 (s), 1170 (s), 1111 (m), 1008 (m). ESI+ mass spectrum (m/z, %): 293 ($[M+Na]^+$, 100%), 271 ($[M+H]^+$, 20%).

2-Methyl-4-(o-nitrobenzenesulfonamidyl)-but-1-en-3-one (**38b**) was obtained as a partially characterised unstable (decomposed fully over two days at room temperature) yellow oil (0.2200 g, 89% yield) from 2-methyl-4-(*o*-nitrobenzenesulfonyl)-but-1-en-3-ol (**37b**; 0.2500 g, 1.40 mmol).

δ_H (400 MHz, $CDCl_3$): 1.85 (3 H, s, CH_3), 4.44 (2 H, d, *J* 4.7, CH_2NH), 5.90 (1 H, s, MeC=CH_2), 5.98 (1 H, s, MeC=CH_2), 6.36 (1 H, s, br, N*H*), 7.71–7.82 (2 H, m, 2 × Ar*H*), 7.92 (1 H, dd, *J* 8.2, 2.1, Ar*H*), 8.03 (1 H, d, *J* 7.7, Ar*H*). δ_C (100 MHz, $CDCl_3$): 17.2 (*C*H_3), 48.7 (*C*H_2), 125.6 (*C*H), 126.3 (*C*H_2), 128.0 (*C*H), 130.4 (q), 131.9 (q), 133.4 (*C*H), 133.6 (*C*H), 142.0 (q), 193.8 (q, *C*=O). υ_{max} (cm^{-1}): 3097 (w), 2926 (m), 1732 (s), 1592 (w), 1543 (s), 1458 (s), 1375 (s), 1250 (m), 1171 (s), 1123 (m), 1024 (s), 930 (m), 757 (s), 669 (m). ESI+ mass spectrum (m/z, %): 307 ($[M+Na]^+$, 80%), 285 ($[M+H]^+$, 45%).

(E)-5-(o-Nitrobenzenesulfonamidyl)-hex-2-en-4-one (**38c**) was obtained as a more stable yellow oil (0.4170 g, 84% yield) from (*E*)-5-(*o*-nitrobenzenesulfonamidyl)-hex-2-en-4-ol (**37c**; 0.5000 g, 1.67 mmol).

δ_H (250 MHz, $CDCl_3$): 1.42 (3 H, d, *J* 7.2, CH_3CH=CH), 1.91 (3 H, dd, *J* 6.9, 1.6, CH_3CHNH), 4.42 (1 H, dq, *J* 7.2, 7.2, C*H*Me), 6.16 (1 H, dd, *J* 15.6, 1.5, MeHC=C*H*), 6.48 (1 H, d, br, *J* 7.2, N*H*), 6.96 (1 H, dq, *J* 15.6, 6.9, Me*H*C=CH), 7.70–7.72 (2 H, m, 2 × Ar*H*), 7.87–7.89 (1 H, m, Ar*H*), 8.04–8.07 (1 H, m, Ar*H*). δ_C (63 MHz, $CDCl_3$): 18.5 (*C*H_3), 19.5 (*C*H_3), 56.5 (*C*H), 125.5 (*C*H), 127.0 (*C*H), 129.9 (q), 130.2 (*C*H), 132.7 (q), 133.5 (*C*H), 134.3 (*C*H), 146.3 (*C*H), 195.8 (q, *C*=O). υ_{max} (cm^{-1}): 3096 (w), 2925 (m), 1712 (s), 1594 (w), 1542 (s), 1442 (s), 1362 (s), 1250 (m), 1172 (s), 1124 (m), 1024 (s), 928 (m), 744 (s), 655 (m). EI+ mass spectrum (m/z, %): 299 ($[M+H]^+$, 1%), 229 (50%), 186 (95%), 156 (5%), 109 (20%), 92 (15%), 77 (20%), 69 (100%), 64 (15%). CI+ mass spectrum (m/z, %): 316 ($[M+NH_4]^+$, 100%), 299 ($[M+H]^+$, 3%). HRMS (CI+): found $[M+NH_4]^+$ 316.0965, $C_{12}H_{14}N_2O_5S$ requires 316.0967.

4.8 *Synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides (39)*

To a solution of the freshly prepared allylic ketone (**38**, ~0.2–0.4 mmol, 1.0 eq) in glacial acetic acid (10 ml) was added gradually, with stirring, zinc powder (~0.2–0.5 g) over a period of 1 hour at room temperature. After addition was complete, the mixture was heated under reflux for an additional 2–4 hours, whilst being monitored by TLC. The crude mixture was filtered, concentrated *in vacuo*, and purified by flash column chromatography (eluent: PE:EtOAc/1:1) to yield the 1,2,5-benzothiadiazepine 1,1-dioxides (**39**), as follows:

2,3,4,5-Tetrahydro-4-ethenyl-1,2,5-benzothiadiazepine 1,1-dioxide (**39a**) was obtained as a yellow solid (0.0413 g, 50% yield) from 4-(*o*-nitrobenzenesulfonamidyl)-but-1-en-3-one (**38a**, 0.1000 g, 0.37 mmol), mp: 133–137 °C.

δ_H (400 MHz, $CDCl_3$): 3.05 (1 H, ddd, *J* 15.1, 7.5, 4.6, CH_2NH), 3.28 (1 H, m, C*H*CH=CH_2), 3.37 (1 H, ddd, *J* 13.1, 7.6, 3.6 CH_2NH), 4.17 (1 H, dd, *J* 7.4, 3.4, CH_2N*H*), 4.83 (1 H, d, *J* 10.3, HC=CH_2), 4.95 (1 H, dd, *J* 16.2, 0.7 HC=CH_2), 5.70 (1 H, bd, *J* 9.8, N*H*CH), 5.8 (1 H, ddd, *J* 15.9, 10.3, 7.9, *H*C=CH_2), 7.73–7.80 (2 H, m, 2 × Ar*H*), 7.83 (1 H, t, *J* 7.8, Ar*H*), 8.10 (1 H, d, *J* 8.2, Ar*H*). δ_C (100 MHz, $CDCl_3$): 47.4 (*C*H_2), 73.4 (*C*H), 112.6 (*C*H_2), 125.3 (*C*H), 130.7 (*C*H), 133.0 (*C*H), 133.3 (*C*H), 133.9 (*C*H), 140.0 (q), 147.8 (q). υ_{max} (cm^{-1}): 3450 (bm), 3363 (bm), 3225 (bm), 2986 (m), 2906 (m), 1604 (m), 1591 (w), 1479 (s), 1145 (s), 1066 (m). ESI+ mass spectrum (m/z, %): 225 ($[M+H]^+$, 100%), 247 ($[M+Na]^+$, 25%). C, H, N (%): found C 53.4, H 5.2, N 12.7; $C_{10}H_{12}N_2O_2S$ requires C 53.6, H 5.4, N 12.5.

2,3,4,5-Tetrahydro-4-(2'-propenyl)-1,2,5-benzothiadiazepine 1,1-dioxide (**39b**) was obtained as a yellow solid (0.0410 g, 49% yield) from 2-methyl-4-(*o*-nitrobenzenesulfonamidyl)-but-1-en-3-one (**38b**, 0.1000 g, 0.35 mmol), mp: 165–167 °C.

δ_H (400 MHz, $CDCl_3$): 1.62 (3 H, s, CH_3), 2.85 (1 H, ddd, *J* 12.9, 8.1, 4.7, CH_2NH), 3.08–3.12 (1 H, m, CH_2NH), 4.04 (1 H, d, *J* 5.6, C*H*NH), 4.88 (1 H, s, MeC=CH_2), 4.96 (1 H, s, MeC=CH_2), 5.00 (1 H, s, br, N*H*), 5.49 (1 H, s, br, N*H*), 6.78–6.81 (2H, m, 2 × Ar*H*), 7.33

(1 H, t, *J* 7.5, Ar*H*), 7.70 (1 H, d, *J* 7.9, Ar*H*). δ_C (100 MHz, $CDCl_3$): 18.3 (*C*H_3), 47.0 (*C*H_2), 73.4 (*C*H), 112.3 (*C*H_2), 117.8 (*C*H), 117.9 (*C*H), 121.4 (q), 129.6 (*C*H), 134.3 (*C*H), 144.0 (q), 145.0 (q). υ_{max} (cm^{-1}): 3478 (bm), 3379 (bm), 3250 (bm), 2970 (m), 2921 (m), 1621 (m), 1600 (m), 1570 (w), 1484 (s), 1455 (m), 1320 (s), 1154 (s), 1059 (m), 909 (m), 754 (s), 696 (m). ESI+ mass spectrum (m/z, %): 239 ([M+H]$^+$, 30%). C, H, N (%): found C 55.4, H 6.0, N 11.7; $C_{11}H_{14}N_2O_2S$ requires C 55.4, H 5.9, N 11.8.

2,3,4,5-Tetrahydro-3-methyl-4-(1'-propenyl)-1,2,5-benzothiadiazepine 1,1-dioxide (**39c**; ~1:1 mixture of diastereoisomers) was obtained as a yellow oil (0.03810 g, 45% yield) from (*E*)-5-(*o*-nitrobenzenesulfonamidyl)-hex-2-en-4-one (**38c**, 0.1000 g, 0.34 mmol).

δ_H (400 MHz, $CDCl_3$): 1.10 (3 H, d, *J* 6.3, C*H*$_3$CHNH), 1.14; 1.18 (3 H, 2 × d, *J* 6.6, HC=CHC*H*$_3$), 3.54; 3.58 (1 H, 2 × m, C*H*Me), 4.6–4.7 (1 H, s, br, N*H*), 4.92 (1 H, d, *J* 7.4, N*H*), 5.01; 5.07 (1 H, 2 × s, C*H*NH), 5.31 (1 H, dq, *J* 15.1, 6.8, MeHC=C*H*), 5.36–5.47 (1 H, m, Me*H*C=C*H*), 6.76 (1 H, d, *J* 8.5, Ar*H*), 6.79 (1 H, t, *J* 8.0, Ar*H*), 7.31 (1 H, t, *J* 7.7, Ar*H*), 7.70 (1 H, d, *J* 7.9, Ar*H*). δ_C (100 MHz, $CDCl_3$): 20.8; 20.9 (*C*H_3), 21.8; 21.9 (*C*H_3), 50.6 (*C*H), 50.8 (*C*H), 117.7 (*C*H), 117.8 (*C*H), 122.6; 122.7 (q), 129.4; 129.5 (*C*H), 132.3; 132.4 (*C*H), 132.5; 132.6 (*C*H), 134.0; 134.1 (*C*H), 134.5; 134.6 (q), 141.6; 144.9 (q). υ_{max} (cm^{-1}): 3476 (bm), 3378 (bm), 3249 (bm), 2979 (m), 2932 (m), 1622 (m), 1601 (m), 1570 (m), 1484 (s), 1455 (s), 1332 (s), 1155 (s), 1061 (m), 971 (m), 755 (s), 698 (m). EI+ mass spectrum (m/z, %): 253 ([M+H]$^+$, 1%), 252 ([M]$^+$, 4%), 172 (15%), 156 (25%), 112 (75%), 108 (30%), 92 (100%), 80 (45%), 65 (98%). ESI+ mass spectrum (m/z, %): 253 ([M+H]$^+$, 40%). HRMS (ESI+): found [M+H]$^+$ 253.1012, $C_{12}H_{16}N_2O_2S$ requires 253.1010.

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References

[1] H. Tucker, D.J. LeCount. In *Comprehensive Heterocyclic Chemistry II*, C.W. Rees, A.R. Katritzky, E.F.V. Scriven (Eds.), pp. 151–182, Elsevier Science, Oxford (1996).
[2] J.T. Sharp. In the *Second Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds*, M. Sainsbury (Ed.), pp. 217–227, Elsevier Science, Amsterdam (1999).
[3] A. Walser, R.I. Fryer. In *Chemistry of Heterocyclic Compounds*, E.C. Taylor, A. Weissberger, (Eds.), pp. 431–946, Wiley, Chichester, UK (1991).
[4] M.F. Cheng, J.M. Fang. *J. Comb. Chem.*, **6**, 99 (2004).
[5] P. Wiklund, M. Rogers-Evans, J. Bergman, *J. Org. Chem.*, **69**, 6371 (2004).
[6] G. Cuny, M. Bois-Choussy, J.P. Zhu. *J. Am. Chem. Soc.*, **126**, 14475 (2004).
[7] K. Hemming, C. Loukou. *Tetrahedron*, **60**, 3349 (2004).
[8] A.P. Alyn, A.S. Trifilenkov, J.A. Kuzovkova, S.A. Kutepov, A.V. Nitikin, A.V. Ivachtchenko. *J. Org. Chem.*, **70**, 1478 (2005).
[9] T. Tsuchiya. In *Comprehensive Heterocyclic Chemistry II*, C.W. Rees, A.R. Katritzky, E.F.V. Scriven (Eds.), pp. 344–346, Elsevier Science, Oxford (1996).
[10] K. Hemming. In *Second Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds*, M. Sainsbury (Ed.), pp. 288–292, Elsevier Science, Amsterdam (1999).
[11] J.T. Sharp. In *Comprehensive Heterocyclic Chemistry*, A.R. Katritzky, C.W. Rees (Eds.), pp. 644–645, Pergamon, New York (1984).
[12] Recent review: K. Hemming, C. Loukou. *J. Chem. Res.*, 1 (2005).
[13] O. Migliara, S. Petruso, V. Sprio. *J. Heterocycl. Chem.*, **16**, 835 (1979).
[14] P.H.L. Wei, S.C. Bell, US patent 3453266 (1969); *Chemical Abstracts*, 71: 91553.

[15] F. Borsini, G. Volterra, A. Lecci, S. Evangelista, A. Mancinelli, C. Cutrufo, M. Parlini, T. Mennini, D. Barone, A. Meli. Arzneim. *Forsch. Drug Res.*, **41(1)**, 573 (1991).
[16] D. Giannotti, G. Viti, P. Sbraci, V. Pestellini, G. Volterra, F. Borsini, A. Meli, P. Dapporto, P. Paoli. *J. Med. Chem.*, **34**, 1356 (1991).
[17] G. Stefancich, R. Silvestri, E. Pagnozzi, M. Artico. *J. Heterocycl. Chem.*, **31**, 867 (1994).
[18] K. Ogawa, Y. Matsushita. *Chem. Pharm. Bull.*, **40**, 2442 (1992).
[19] R.J. Cherney, D.T. Maeyer, L. Wang, J.J.W. Duan, L.H. Chen, E.C. Arner, B.D. Jaffe, M.B. Covington, C.P. Decicco. *Abstracts of Papers of the American Chemical Society*, **218**, abstract 87-Medi (1999).
[20] J.J.W. Duan, L.H. Chen, C.P. Decicco, R.J. Cherney, Z.R. Wasserman, K.E. Kennedy, D.T. Maeyer, L. Wang, M.E. Voss, K.D. Hardman, E.C. Arner, M.B. Covington, R.R. Liu. *Abstracts of Papers of the American Chemical Society*, **218** (1999).
[21] K. Leftheris, J.T. Hunt, C.Z. Ding, US patent 6156746 (2000); *Chemical Abstracts*, 134: 29439.
[22] R.J. Cherney, J.J.-W. Duan, M.E. Voss, L. Chen, L. Wang, D.T. Meyer, Z.R. Wasserman, K.D. Hardman, R.-Q. Liu, M.B. Covington, M. Qian, S. Mandlekar, D.D. Christ, J.M. Trzaskos, R.L. Magolda, R.R. Wexler, C.P. Decicco. *J. Med. Chem.*, **46**, 1811 (2003).
[23] M. Artico, R. Silvestri, E. Pagnozzi, G. Stefancich, S. Massa, A.G. Loi, M. Putzolu, S. Corrias, M.G. Spiga, P. La Colla. *Bioorg. Med. Chem.*, **4**, 837 (1996).
[24] M. Artico, R. Silvestri, E. Pagnozzi, G. Stefancich, S. Massa, A.G. Loi, M. Putzolu, S. Corrias, M.G. Spiga, P. La Colla, D. Lichino. *Farmaco*, **51**, 425 (1996).
[25] R. Costi, R. Di Santo, M. Artico, S. Massa, M.E. Marongiu, A.G. Loi, A. De Montis, P. La Colla. *Antiviral Chem. Chemotherapy*, **9**, 127 (1998).
[26] D. Giannotti, G. Viti, R. Nannicini, V. Pestellini, D. Bellarosa, *Bioorg. Med. Chem. Lett.*, **5**, 1461 (1995).
[27] D. Bellarosa, G. Antonelli, F. Bambacioni, D. Giannotti, G. Viti, R. Nannicini, A. Giachetti, F. Dianzani, M. Witvrouw, R. Pauwels, J. Desmyter, E. De Clercq. *Antiviral Res.*, **30**, 109 (1996).
[28] R. Silvestri, M. Artico, E. Pagnozzi, G. Stefancich, S. Massa, P. La Colla, A.G. Loi, M.G. Spiga, S. Corrias, D. Lichino. *Farmaco*, **51**, 425 (1996).
[29] R. Costi, R. Di Santo, M. Artico, S. Massa. *J. Heterocycl. Chem.*, **39**, 81 (2002).
[30] K. Hemming, N. Patel. *Tetrahedron Lett.*, **45**, 7553 (2004).
[31] F. Chimenti, S. Vomero, V. Nacci, M. Scalzo, R. Giuliano, M. Artico. *Farmaco* (Ed. Sci.), **29**, 589 (1974).
[32] N. Langlois, R.Z. Andriamialisoa. *Heterocycles*, **29**, 1529 (1989).
[33] D.E. Thurston, D.S. Bose. *Chem. Rev.*, **94**, 433 (1994).
[34] R. Silvestri, M. Artico, E. Pagnozzi. *J. Heterocycl. Chem.*, **31**, 1033 (1994).
[35] R. Di Santo, R. Costi, M. Artico, S. Massa. *J. Heterocycl. Chem.*, **33**, 2019 (1996).
[36] R. Di Santo, R. Costi, M. Artico, S. Massa. *Farmaco*, **52**, 375 (1997).
[37] R. Silvestri, A. Pifferi, G. De Martino, S. Massa, C. Saturnino, M. Artico. *Heterocycles*, **53**, 2163 (2000).
[38] G.F. Field, W.J. Zally, L.H. Sternbach. *J. Org. Chem.*, **36**, 2968 (1971).
[39] K. Ogawa, Y. Matsushita. *Chem. Pharm. Bull.*, **40**, 2442 (1992).
[40] M. Artico, R. Silvestri, G. Stefancich. *Synth. Commun.*, **22**, 1433 (1992).
[41] C.W. Whitehead, J.J. Traverso. *J. Org. Chem.*, **28**, 743 (1963).
[42] O. Migliara, S. Petruso, V. Sprio. *J. Heterocycl. Chem.*, **16**, 833 (1979).
[43] T.M. Krülle, J.C.H.M. Wijkmans. *Tetrahedron*, **57**, 7021 (2001).
[44] B. Anwar, P. Grimsey, K. Hemming, M. Krajniewski, C. Loukou. *Tetrahedron Lett.*, **51**, 10107 (2000).
[45] K. Hemming, C. Loukou, S. Elkatip, R.K. Smalley. *Synlett*, 101 (2004).
[46] D.A. Evans, G.C. Andrews. *J. Am. Chem. Soc.*, **94**, 3672 (1972).
[47] D.A. Evans, G.C. Andrews, C.L. Sims. *J. Am. Chem. Soc.*, **93**, 4956 (1971).
[48] S.M. Weinreb. *Acc. Chem. Res.* **21**, 313 (1988).
[49] D.L. Boger, S.M. Weinreb. In *Hetero Diels-Alder Methodology in Organic Synthesis*, pp. 1–33, Academic Press, London (1987).
[50] E.S. Levchenko, Y.G. Bal'on, A.A. Kisilenko. *J. Org. Chem. USSR* (English Transl.), **1(I)**, 151 (1965).
[51] G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H.P. Patzschke, H. Smalla, A. Trede. *Angew. Chem. Int. Ed. Engl*., **1**, 89 (1962).
[52] G. Kresze, W. Wucherpfennig. Angew. *Chem. Int. Ed. Engl.*, **6**, 149 (1967).
[53] R. Bussas, G. Kresze, H. Münsterer, A. Schwöbel. *Sulfur Rep.*, **2**, 215 (1983).
[54] R.S. Garigipati, A.J. Freyer, R.R. Whittle, S.M. Weinreb. *J. Am. Chem. Soc.*, **106**, 7861 (1984).
[55] G.R. Heintzelman, P. Masood, S.M. Weinreb. *Synlett*, 551 (1993).
[56] S.W. Remiszewski, T.R. Stouch, S.M. Weinreb. *Tetrahedron*, **41**, 1173 (1985).
[57] For a review of azide chemistry, see: E.F.V. Scriven, K. Turnbull. *Chem. Rev.*, **88**, 297 (1988).
[58] B.M. Trost, W.H. Pearson. *J. Am. Chem. Soc.*, **103**, 2483 (1981).
[59] B.M. Trost, W.H. Pearson. *J. Am. Chem. Soc.*, **105**, 1054 (1983).
[60] B.M. Trost, W.H. Pearson. *Tetrahedron Lett.*, **24**, 269 (1983).
[61] G.W. Kabalka, G. Li. *Tetrahedron Lett.*, **38**, 5777 (1997).
[62] For a review of the Staudinger reaction, see: Y.G. Gololobov, L.F. Kasukhin. *Tetrahedron*, **48**, 1353 (1992).
[63] E. Fabiano, B.T. Golding, M.M. Sadeghi. *Synthesis*, 190 (1987).
[64] A.R. Katritzky, S. Jiang, L. Urogdi. *Tetrahedron Lett.*, **30**, 3303 (1989).
[65] K. Hemming, M.J. Bevan, C. Loukou, S.D. Patel, D. Renaudeau. *Synlett*, 1565 (2000).
[66] T. Schoetzau, T. Holletz, D. Cech. *Chem. Commun.*, 387 (1996).