Synthetic approaches to 1,2,5-benzothiadiazepine 1,1-dioxides – sulfonamide analogues of the 1,4-benzodiazepines

Karl Hemming* and Christina Loukou

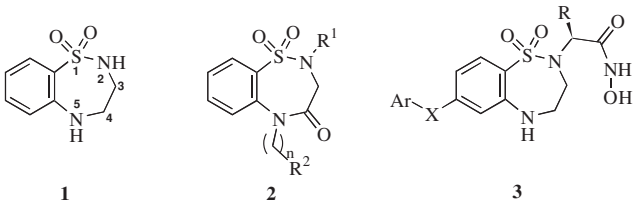
Department of Chemical and Biological Sciences, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, UK

Synthetic approaches to the 1,2,5-benzothiadiazepine 1,1-dioxides, sulfonamide analogues of the 1,4-benzodiazepines, are reviewed. The review incorporates the synthesis of bicyclic, tricyclic and tetracyclic systems, and includes approaches to sulfonamide analogues of the antitumour pyrrolobenzodiazepines, sulfonamide analogues of the tricyclic non-nucleosidic reverse transcriptase inhibiting benzodiazepines (such as nevirapine), and other systems of biological interest. Details of the reactions and biological activity of the 1,2,5-benzothiadiazepines are also given.

Keywords: benzothiadiazepine, 1,4-benzodiazepine, pyrrolobenzodiazepine, pyrrolobenzothiadiazepine, sulfonamide

1. Introduction and scope

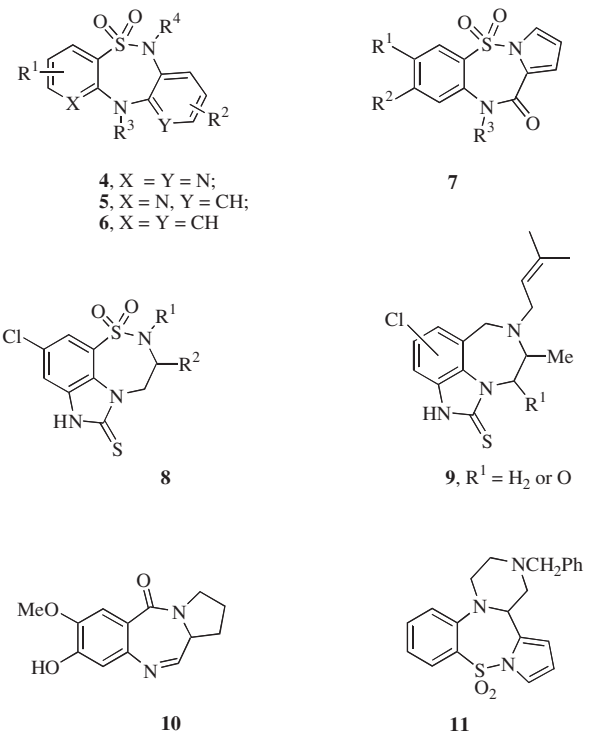
Whilst the synthesis and the biological applications of the 1,4-benzodiazepine pharmacophore continue to attract enormous attention in the literature, the corresponding 1,2,5-benzo-thiadiazepine 1,1-dioxide[1-3] nucleus (**1**) has been subject to less scrutiny. 1,2,5-Benzothiadiazepine 1,1-dioxides are 1,4-benzodiazepine analogues possessing a sulfonyl moiety at the 5-position of the 7-membered benzothiadiazepine ring, and have attracted attention[4-9] as analogues of the benzodiazepines because of their CNS,[4] diuretic,[4a] hypolipidemic,[5] and antiarrhythmic[6] activities, their ability to inhibit metalloproteinase and farnesyl protein transferase enzymes,[7] and their activity as potent tumour necrosis factor-α (TNF-α) converting enzyme (TACE) inhibitors.[8] Some typical examples are the antiarrythmic agents (**2**)[6] and the TACE inhibitors (**3**),[8] as shown in Fig. 1.



1 **2** **3**

Fig. 1

Reports on the synthesis and biological activity of tricyclic analogues are common, with the use of dibenzo- systems as antidepressives[10] and with particular emphasis on the use of dibenzo-[11] or pyridobenzo-[11] and pyrrolobenzothiadiazepine[12-14] non-nucleoside reverse transcriptase inhibitors, with potential for the treatment of AIDS. After the discovery of nevirapine,[15] a search for novel non-nucleoside agents capable of inhibiting the reverse transcriptase (RT) enzyme led to the synthesis of various derivatives of tricyclic systems incorporating a thiadiazepine moiety, such as the dipyrido- (**4**), pyridobenzo- (**5**), and dibenzo- 1,2,5-thiadiazepine analogues (**6**), which together with the pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines (PBTDs) (**7**),[12-14] have exhibited anti-HIV-1 activity. Benzothiadiazepine analogues (**8**) of the anti-HIV drug TIBO (**9**) with specific anti-HIV type 1 activity have also been synthesised.[16]



4, X = Y = N;
5, X = N, Y = CH;
6, X = Y = CH

7

8

9, $R^1 = H_2$ or O

10 **11**

Fig. 2

Pyrrolobenzothiadiazepines (**7**) have also been synthesised as parts of programmes devised to access analogues of the potent antitumour antibiotic pyrrolobenzodiazepines of which DC-81 (**10**) is typical.[17] Tetracyclic pyrrolobenzothiadiazepine derivatives (**11**), which are analogues of the antidepressant aptazepine, have also attracted attention.[18]

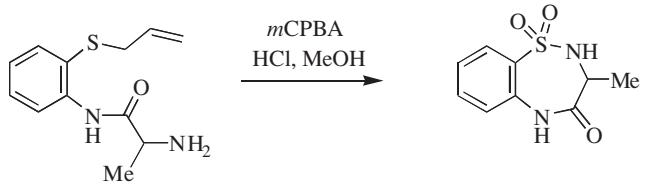
The synthesis of 1,2,5-benzothiadiazepines has been reviewed before only partially and as part of larger reviews covering diazepine heterocycles[1-3] in general. This review will therefore detail all the major methods of synthesis according to the final bond that is formed (1,2; 2,3; 4,5, *etc*), and by other methods such as ring expansion and modification of existing 1,2,5-benzothiadiazepines. This latter section necessarily encompasses key reactions of the 1,2,5-benzothiadiazepines. The review will include approaches not only to the simple bicyclic 1,2,5-benzothiadiazepines, but also to tricyclic and tetracyclic systems which incorporate a 1,2,5-benzothiadiazepine moiety, as these systems have attracted widespread interest as discussed above.

* Correspondent. E-mail: k.hemming@hud.ac.uk

2. Synthesis

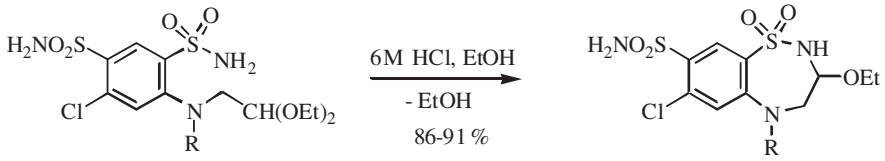
2.1 *Synthesis by 1,2 bond formation*

Intramolecular sulfonamide bond formation is a rare approach. Thus, treatment of the allyl phenyl sulfide (**12**) with *m*-chloroperbenzoic acid in concentrated hydrochloric acid and methanol generated the 1,2,5-benzothiadiazepin-4-ones (**13**) (Scheme 1).[6,19] The reaction proceeds by oxidation of the sulfur, epoxidation of the alkene, and cyclisation where the 1,2-bond formation is accompanied by the elimination of a three carbon leaving group.



12 **13**

Scheme 1



14 **15**

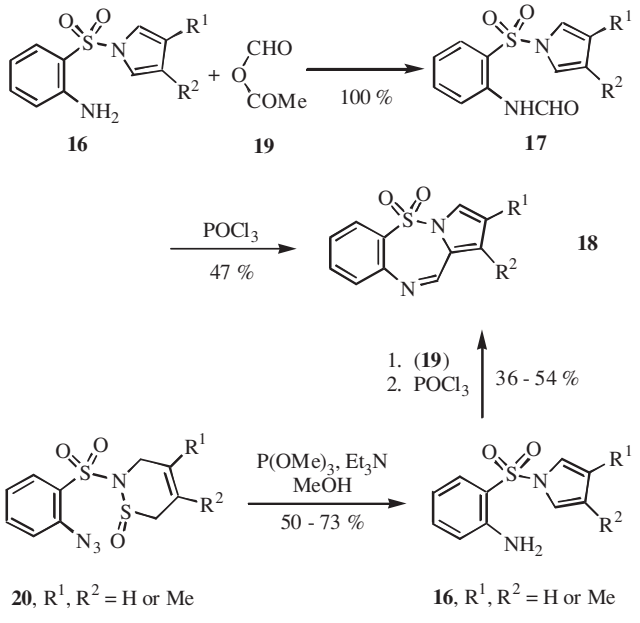
Scheme 2

2.2 *Synthesis by 2,3 bond formation*

Ring closure by nucleophilic attack of the sulfonamide nitrogen onto an electrophilic carbon has been utilised to construct the 2,3 C–N bond, but represents another little-used approach. Thus, treatment of the *N*-β,β-diethoxyethyl-*N*-methyl- and *N*-benzylanilines (**14**) with acid resulted in an intramolecular elimination of ethanol to produce the corresponding 1,2,5-benzothiadiazepine 1,1-dioxides (**15**) in high yields (Scheme 2).[20]

2.3 *Synthesis by 3,4 bond formation*

This bond formation methodology is limited to the synthesis of pyrrolobenzothiadiazepines which, by virtue of the pyrrole ring, possess the necessary reactive carbon that becomes the 3-position of the 1,2,5-benzothiadiazepine ring. Thus, Artico and co-workers[21] constructed the pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-1,1-dioxide (**18**, $R^1 = R^2 = H$) (Scheme 3) in 47 % yield *via* a phosphorus oxychloride mediated Bischler-Napieralski cyclisation reaction of the formylated precursor 1-(2-formamidobenzenesulfonyl)pyrrole (**17**). Precursor (**17**) was derived quantitatively from the reaction of acetic formic anhydride (**19**) with 1-(2-aminobenzenesulfonyl) pyrrole (**16**),[21] which was in turn readily available from the reaction of the corresponding sulfonyl chloride with pyrrole. This *N*-formylation/Bischler-Napieralski ring closure methodology has recently been utilised with similar success by other workers, who were able to access the requisite 1-(2-amino-benzenesulfonyl)pyrroles (**16**) from the 2-(*o*-azidoben-zenesulfonyl)-1,2-thiazine 1-oxides (**20**), also shown in Scheme 3.[22] This key transformation proceeds *via* a trimethyl phosphite mediated ring contraction and desulfurisation of the 1,2-thiazine 1-oxide and is accompanied by the concomitant conversion of the azide into an amine *via* Staudinger reaction and hydrolysis.[23] Formylation and phosphorus oxychloride mediated ring closure proceeded in similar overall yield to that reported by Artico and coworkers.



16 **19** **17** **18**

20, R^1, R^2 = H or Me **16**, R^1, R^2 = H or Me

Scheme 3

2.4 *Synthesis by 4,5 bond formation*

The scarcity of methodologies that exist for the formation of 1,2,5-benzothiadiazepines *via* the formation of other bonds discussed above is explained by the popularity and ease by which they can be constructed by 4,5 C–N formation, by far the most common approach. Due to the plethora of such approaches, this section is divided into sub-sections dealing with the most popular approaches, namely direct intramolecular reductive cyclisation of 2-nitrobenzene-sulfonamido carbonyl compounds, synthesis *via* cyclisation of isolable 2-nitrobenzenesulfonamido carbonyl compounds, and less common approaches such as aza-Wittig methods, and other, non-carbonyl compound based methodologies.

2.4.1 *Direct intramolecular cyclisation of 2-nitrobenzenesulfonamido carbonyl compounds*

The ease of accessibility of the starting materials means that the reduction of 2-nitrobenzenesulfonamides and *in situ* cyclisation of the resultant amine onto a pendant carbonyl group is an extremely popular approach. Thus, reduction of the 2-nitrobenzenesulfonamide derivative (**21**) with zinc-powder in acetic acid resulted in a mixture of the unsaturated 2,3-dihydro-1,2,5-benzothiadiazepine 1,1-dioxide (**22**) and the fully reduced, saturated 2,3,4,5-tetrahydro-1,2,5-benzo-thiadiazepine 1,1-dioxide (**23**), which were easily separated (Scheme 4).[4a]

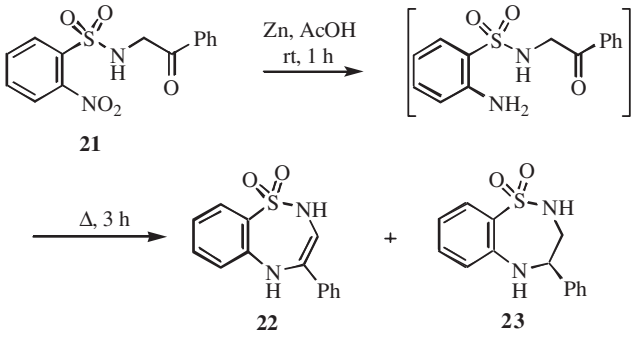
By using catalytic hydrogenation, other workers have isolated the 4-hydroxy-1,2,5-benzothiadiazepine (**25**) in 60

% yield from the reduction and *in situ* cyclisation of the 2-nitro-benzenesulfonamide derivative (**24**) (Scheme 5).[24] The cyclisation proceeded with concomitant reduction of the alkene side chain and produced only a single diastereoisomer.

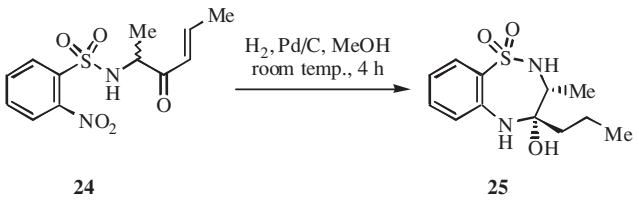
With the aim of finding novel antiarrythmic agents, Ogawa and Matsushita[6] produced numerous 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-dioxides, including the parent system (**27**), which was synthesised in moderate yield *via* reduction of *N*-(2-nitrobenzenesulfonyl)glycine (**26**) with zinc powder in acetic acid and subsequent cyclisation of the non isolable intermediate aniline (Scheme 6).

The nitro carbonyl group cyclisation approach to the tricyclic pyrrolobenzothiadiazepines was first described by Chimenti *et al*.[17] Thus, as shown in Scheme 7, reduction of the nitro group in compound (**28**) with hydrogen in the presence of platinum oxide as a catalyst was accompanied by cyclisation to afford directly the pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-1,1-dioxide (**29**), with no over-reduction. Later, Artico and coworkers[21] showed that iron powder–acetic acid reduction of compound (**28**) gave the pyrrolobenzothiadiazepine (**29**), also directly, but in an improved 92 % yield.

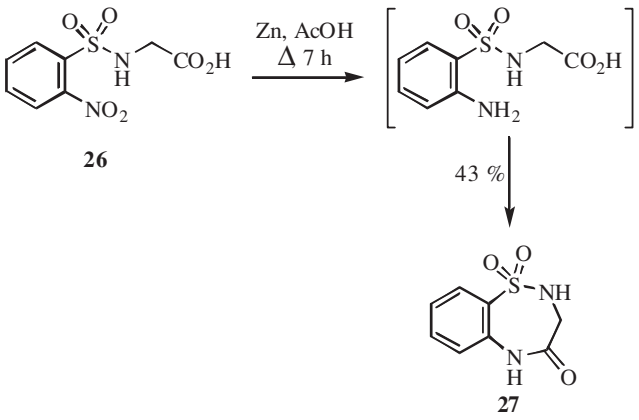
A further reductive cyclisation approach to the pyrrolobenzothiadiazepine nucleus was reported by the same group[25] using glyoxic esters as the pendant carbonyl functionality.



Scheme 4



Scheme 5



Scheme 6

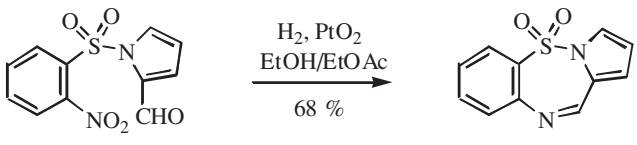
Thus, treatment of the glyoxic ester derivative (**30**) with iron powder in acetic acid under reflux led to the quantitative formation of the pyrrolobenzothiadiazepine (**31**) (Scheme 8), a procedure which again left the newly formed imine bond intact.

Reduction with zinc in acetic acid can lead to complete over-reduction. Thus, in a novel nitro-reduction carbonyl group cyclisation approach, shown in Scheme 9, the alkenyl nitrobenzenesulfonamide (**32**) was subjected to an initial ozonolysis in order to produce the aldehyde (**33**). Subsequent reductive cyclisation of compound (**33**) with zinc in acetic acid under reflux gave the 1,2,5-benzothiadiazepine (**34**) in 18 % overall yield.[8] The products were transformed into benzothiadiazepine hydroxamates (**3**) [see Fig. 1, Section 1] for use as selective tumour necrosis factor-α (TNF-α) converting enzyme inhibitors.[8]

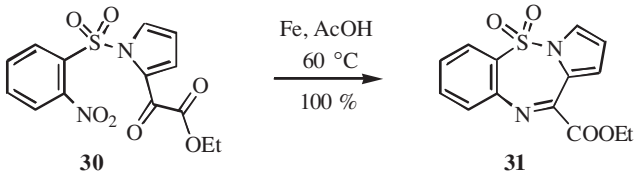
2.4.2 *Synthesis from isolable 2-aminobenzene-sulfonamido carbonyl compounds*

The methods discussed in Section 2.4.1 involved proposed, though non-isolable, 2-aminobenzenesulfonamide derivatives as intermediates, where cyclisation onto the pendant carbonyl group was spontaneous. The precursors to these amino intermediates are the corresponding 2-nitrobenzenesulfonamides and the reductive conditions employed mean that the isolation of the amino intermediates under the conditions of reductive-cyclisation is often not possible as intramolecular cyclisation of the amine onto the carbonyl group is often immediate when the pendant carbonyl group is an aldehyde or ketone. However, careful work by Langlois and Andriamialisoa[26] (Scheme 10) was able to show that the pyrrolidino 2-aminobenzenesulfonamide (**36**) could be isolated upon Raney nickel reduction of the precursor nitro compound (**35**). Subsequent cyclisation of intermediate (**36**) in an acidic medium gave the desired pyrrolidinobenzothiadiazepines (**37**), which are analogues of the pyrrolobenzodiazepine antitumour, antibiotic natural product abbeymycin.[27] These natural products derive their antitumour activity from the ability to form a covalent bond with *N*-guanine residues in the DNA minor grove.[27] Hence, the presence of the electrophilic centre at position 4 of the 1,2,5-benzothiadiazepine ring in compound (**37**) was a necessary feature of the synthesis, and it was therefore necessary that direct cyclisation, and potential over-reduction, of compound (**35**) was carefully avoided by ensuring that the amino compound (**36**) was isolated and cyclised in a separate, non-reductive, step.

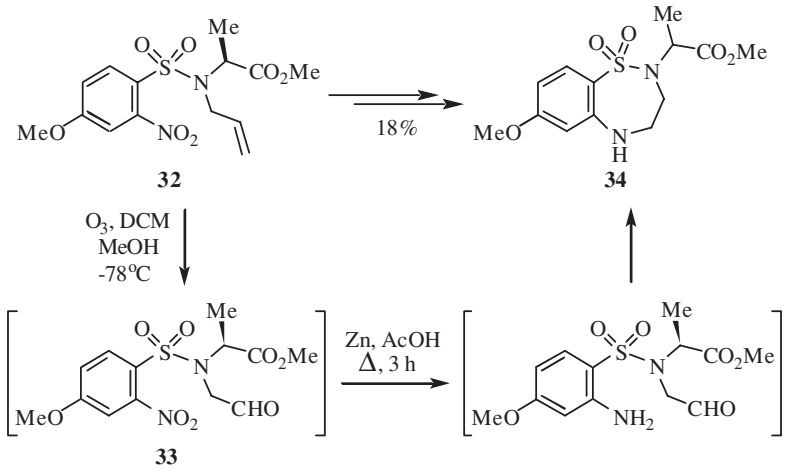
The 2-aminobenzenesulfonamide intermediates are much easier to isolate when the pendant carbonyl group is an ester, owing to the presence of the relatively unreactive ester group



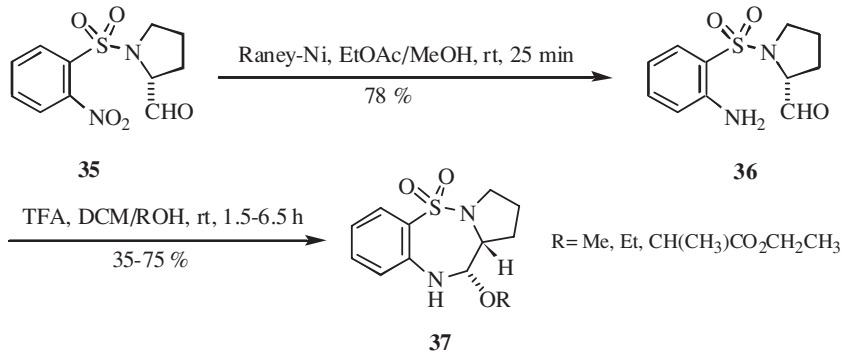
Scheme 7



Scheme 8



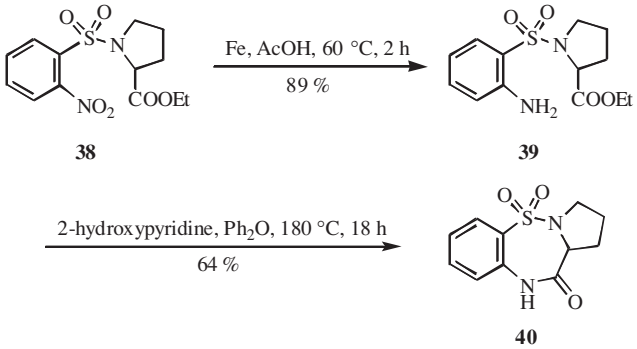
Scheme 9



Scheme 10

which usually requires further manipulation before it will react with an arylamine. Thus, Artico *et al*.[13] reported the synthesis of pyrrolidinobenzothiadiazepin-4-one derivative (**40**) starting from 2-ethoxycarbonyl-1-(2-nitrobenzene-sulfonyl)pyrrolidine (**38**), which was reduced to the corresponding amino compound (**39**) with iron powder in acetic acid (Scheme 11). Intramolecular cyclisation of the aniline (**39**) was achieved by heating in the presence of 2-hydroxypyridine to afford the target compound (**40**).

The pyrrolobenzodiazepine antitumour natural products are thought to require the presence of a saturated pyrrole ring (*i.e*. a pyrrolidine) for antitumour activity,[27] and the pyrrolobenzothiadiazepine syntheses detailed in Schemes 10 and 11 take heed of this requirement. However, pyrrolobenzothiadiazepines with intact pyrrole rings have enjoyed attention in the search for non nucleosidic reverse transcriptase inhibitors.

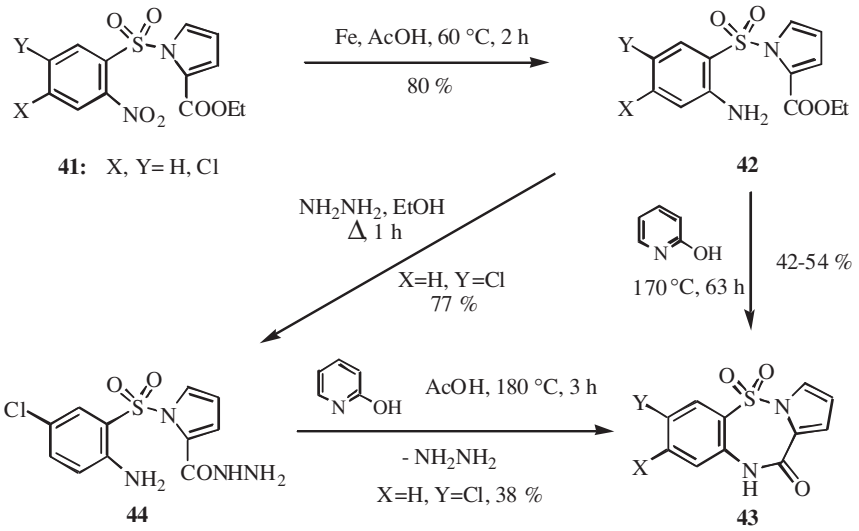


Scheme 11

Thus, the synthesis of pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-4-one 1,1-dioxides (**43**) in 42–54 % yield *via* intramolecular cyclisation of the ester (**42**) has been reported,[13,19] again using 2-hydroxypyridine to facilitate amide bond formation (Scheme 12). The starting compounds (**42**) were isolated in high yield by reduction of the corresponding nitro compound (**41**) on heating in the presence of iron in acetic acid. Furthermore, when 1-(2-amino-5-chlorobenzenesulfonyl) pyrrole-2-carbohydrazide (**44**), prepared in high yield *via* the reaction of ester (**42**, X=H; Y=Cl) with hydrazine, was treated with 2-hydroxypyridine, the pyrrolobenzothiadiazepin-4-one (**43**, X = H; Y = Cl) was obtained in moderate yield (Scheme 12),[28] after loss of hydrazine.

Deprotection of the Fmoc protected amines (**45**) with di*iso*propylethylamine (DIEA) in dichloromethane resulted in cyclisation to give the unexpected 3-hydroxy-1,2,5-benzothiadiazepines (**47**) *via* the deprotected intermediate amine as shown in Scheme 13.[29] Standard deprotection of compound (**45**) with, for example, piperidine, was unsuccessful due to competing Michael addition, hence necessitating the use of the hindered tertiary base DIEA. The 3-hydroxy-1,2,5-benzothiadiazepines (**47**) were proposed to have arisen from a series of tautomerisms (see Scheme 13) to give the intermediate (**46**), whose formation was followed by cyclisation and elimination of water to form the 4,5 C=N bond. Finally, the re-addition of the eliminated water across the 2,3 C=N bond put in place the 3-hydroxy group.

An approach to the acetyl-substituted derivative (**49**) was established[4a] by a route starting from 2-amino-*N*-(2'-acetimidoylacetamyl)benzenesulfonamide (**48**), which cyclised in acid to generate the 3-acetyl-1,2,5-benzothiadiazepine (**49**) (Scheme 14), after hydrolysis of the imine group.



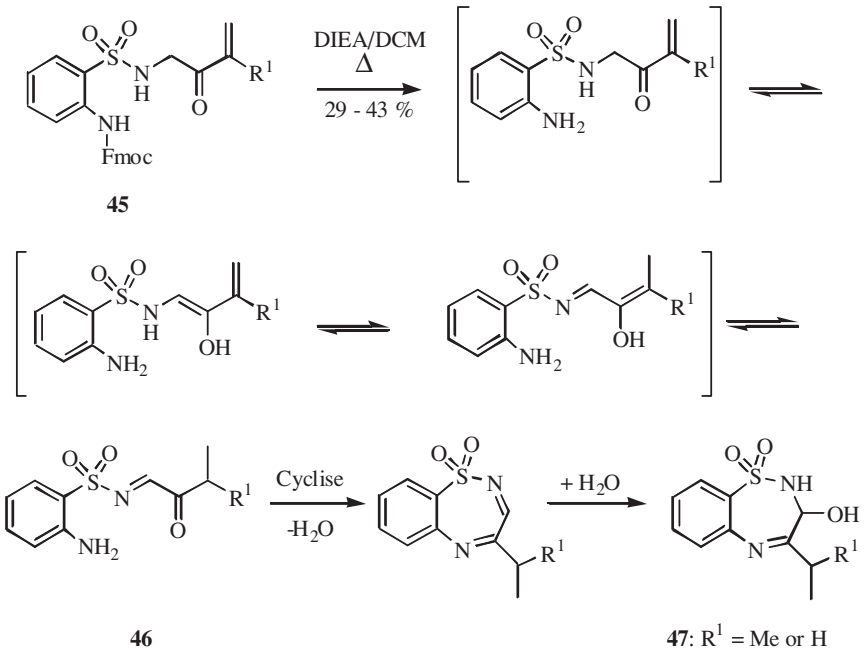
Scheme 12

2.4.3 *Aza-Wittig cyclisation*

Aza-Wittig cyclisation is a common approach to benzodiazepine heterocycles[30] and this methodology has also been applied to the synthesis of 1,2,5-benzothiadiazepines.[31] Thus, as shown in Scheme 15, aza-Wittig cyclisation of the iminophosphoranyl ketone precursor (**52**) gave the C4–N5 unsaturated 1,2,5-benzothiadiazepines (**53**) in 49–63 % yield, including the tricyclic system (**54**). The neutral conditions of the aza-Wittig reaction presumably aid the retention of the double bond in the 4,5-position rather than allowing the tautomerism into the 3,4-position, as seen in Schemes 4 and 14, for example. This methodology hence provides the ability to control exactly the position of the new double bond, a feature often not available *via* the classical amine-carbonyl group cyclisation where double bond shifts are possible. The iminophosphoranyl ketone precursors (**52**) required for this work were synthesised from the corresponding alcohols (**51**), which were in turn available from the 2-(*o*-azidobenzenesulfonyl)-1,2-thiazine 1-oxides (**50**) *via* Staudinger reaction with a phosphine[23] (to install the iminophosphorane group) and conversion of the 1,2-thiazine-1-oxide ring into the vicinal sulfonamido alcohol (**51**) using the reaction sequence[32] shown in Scheme 15.

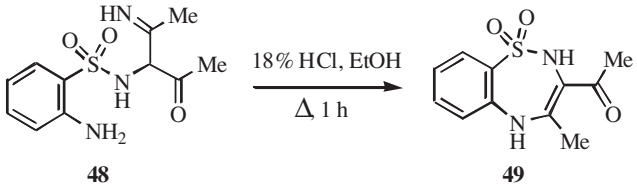
2.4.4 *Non-carbonyl group based methods for 4,5 C–N bond formation*

A few approaches do not rely upon cyclisation onto a carbonyl group. Studies by Krülle and Wijkmans[9] described the synthesis of 3-methoxycarbonyl-2-*N*-methyl-1,2,5-benzothiadiazepine 1,1-dioxides (**57**) *via* an alkoxide-catalysed intramolecular Michael addition of dehydroalanine derivative (**56**) (Scheme 16). The synthesis was achieved *via* Fmoc-deprotection of compound (**55**), by heating in a 1:1 solution of dichloromethane and *N*,*N*-di*iso*propylethylamine (DIEA), to afford the aniline derivative (**56**) in 70 % yield. DIEA was used as the base during the Fmoc deprotection step since the commonly used secondary amines underwent competitive Michael addition to the α,β-unsaturated ester. Subsequent cyclisation with sodium *t*-butoxide in tetrahydrofuran furnished the desired 1,2,5-benzothiadiazepine 1,1-dioxide (**57**) as the sole product in 60 % yield.[9]



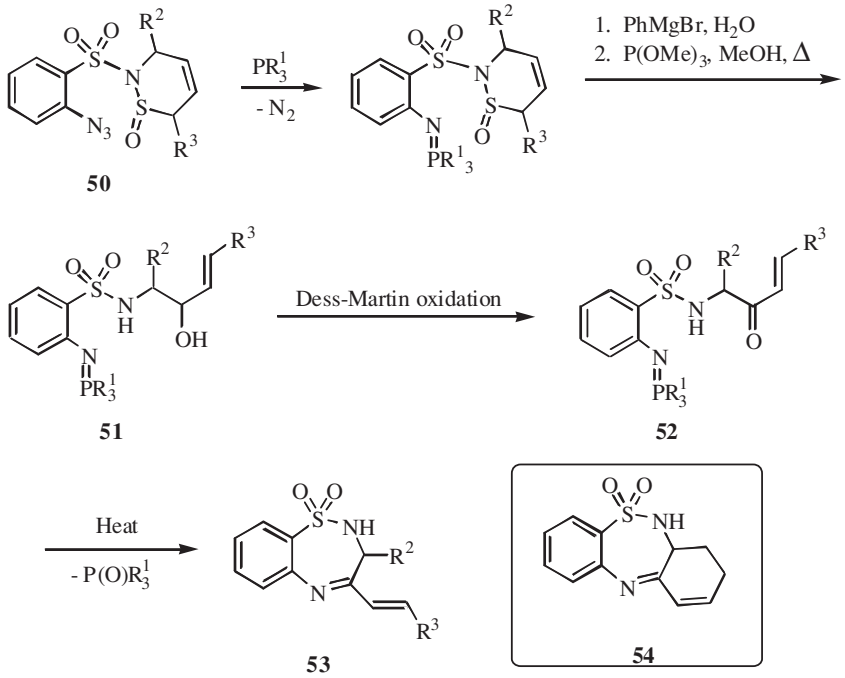
Scheme 13

Nucleophilic substitution by reaction of an amine with a primary alkyl bromide has been use to construct 1,2,5-benzothiadiazepines. Hence, the reduction of the nitro compound (**58**, X = OBn) (Scheme 17) using iron in acetic acid gave the aniline (**59**), which, on heating with 4-methylmorpholine in DMF, underwent cyclisation to form the 1,2,5-benzothiadiazepine 1,1-dioxide (**60**, X = OBn) in 75 % yield.[8] The treatment of the dinitro compound (**58**, X = NO_2) with iron in acetic acid under the same conditions resulted in the reduction of both of the nitro groups to form the intermediate aniline (**59**, X = NH_2), which underwent cyclisation on heating with 4-methylmorpholine in DMF, to afford the 1,2,5-benzothiadiazepine 1,1-dioxide (**60**, X = NH_2) in 43 % overall yield (Scheme 17).[8]



48 **49**

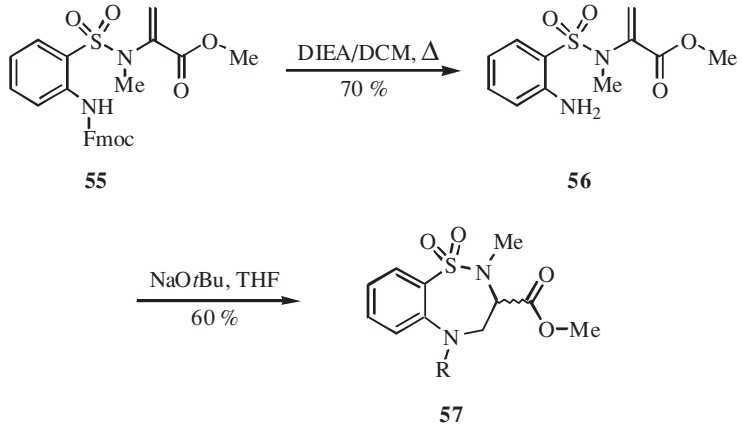
Scheme 14



50 **51** **52** **53** **54**

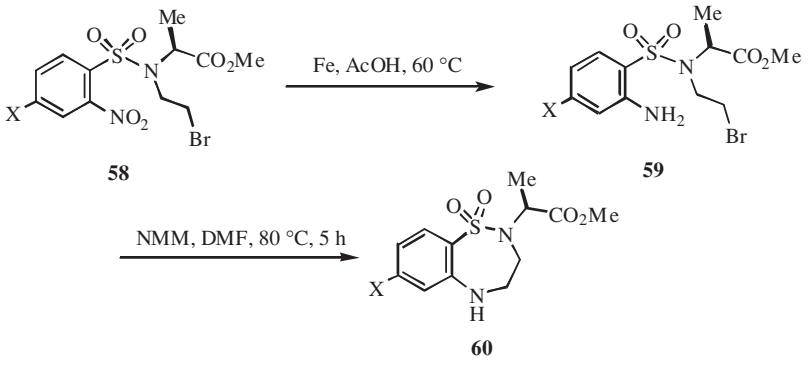
Scheme 15

Nucleophilic aromatic substitution has been used during the synthesis of a series of 6,11-dihydrodibenzo[*c*,*f*][1,2,5]t hiadiazepin-5,5-dioxides (**63**),[10b] which were evaluated for potential antidepressant activity. As shown in Scheme 18, the reduction of the *N*-(2'-halophenyl)-2-nitrobenzenesulfonamides (**61**) with iron in acetic acid under reflux followed by *in-situ* acetylation with acetic anhydride gave the *N*-(2'-halophenyl)-2-(acetylamino)benzenesulfonamides (**62a**, R^1 = H, R^2 = COMe), which were *N*-alkylated to give the *N*-(2'-halophenyl)-*N*-alkyl-2-(acetylamino)benzenesulfonamides (**62b**, R^1 = alkyl; R^2 = COMe). Subsequent cyclisation in the presence of potassium carbonate, copper powder and cuprous bromide in DMF at reflux gave the dibenzo[*c*,*f*][1,2,5]thiadi azepin-5,5-dioxides (**63**). The pyrido[3,2-c][1,2,5]benzothiadiazepines (**64**) were synthesised in the same manner starting from the *N*-(2'-halopyridyl)-*N*-alkyl-2-benzenesulfonamides (**62c**) (Scheme 18).[11b]

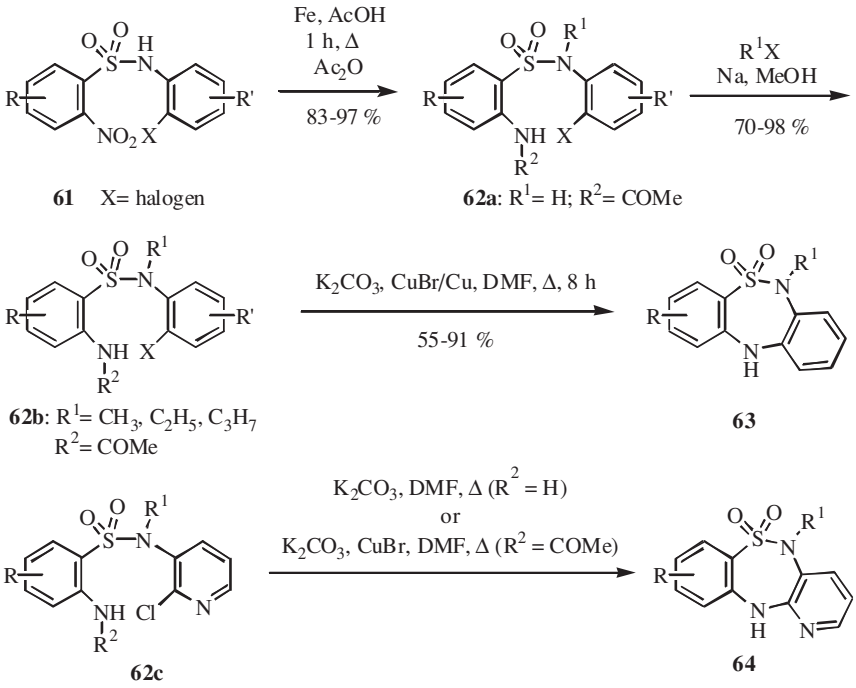


55 **56** **57**

Scheme 16



Scheme 17

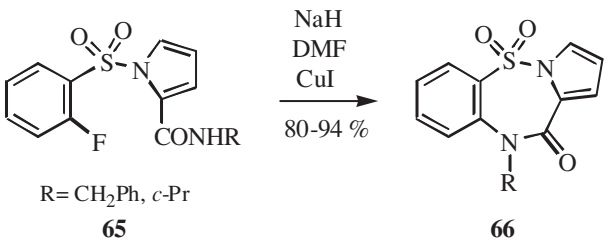


Scheme 18

2.5 *Synthesis by 5,6 bond formation*

5-Benzyl- (**66,** R=PhCH$_2$) and 5-cyclopropyl- (**66**, R=*c*-Pr) substituted pyrrolobenzothiadiazepin-4-one derivatives have been obtained in high yields (80–94 %) by intramolecular nucleophilic aromatic substitution mediated cyclisation of 1-(2-fluorobenzenesulfonyl)-1*H*-pyrrole-2-carboxamides (**65**, R=PhCH$_2$ or cyclopropyl) in the presence of sodium hydride and cuprous iodide (Scheme 19).[13]

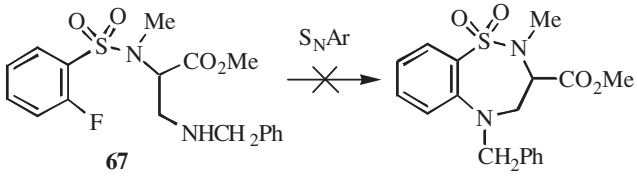
Interestingly, Krülle and Wijkmans noted that the 2-fluorobenzenesulfonyl compound (**67**) did not undergo intramolecular nucleophilic aromatic substitution either under similarly typical S_NAr conditions, or upon thermolysis (Scheme 20).[9]



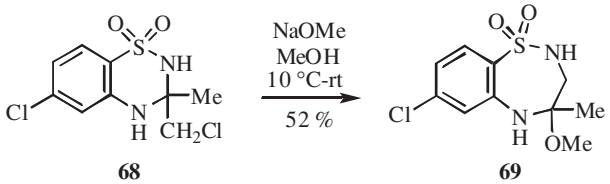
Scheme 19

2.6 *Synthesis by ring expansion*

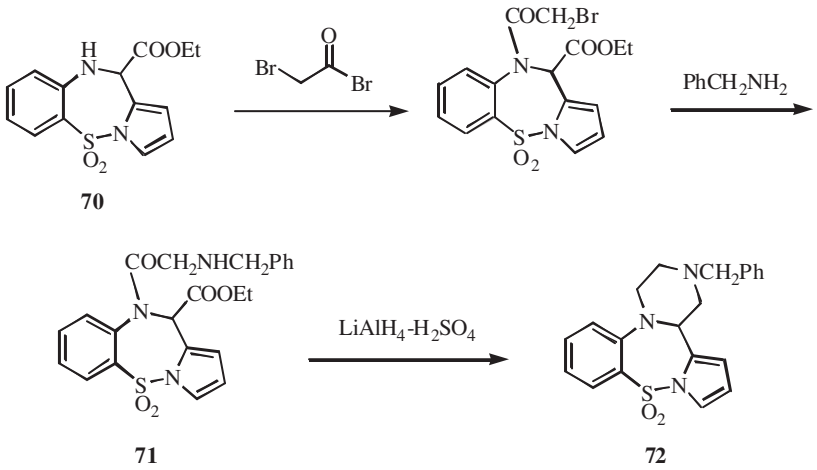
Sternbach and co-workers[33] reported the ring expansion of chloromethylbenzothiadiazines as a means to synthesise 1,2,5-benzothiadiazepines. As an example, treatment of 3-chloromethyl-1,2,4-benzothiadiazine 1,1-dioxide (**68**) with sodium methoxide in methanol gave 2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine 1,1-dioxide (**69**) in 52 % yield (Scheme 21).



Scheme 20



Scheme 21



Scheme 22

2.7 *Synthesis from the reactions of other 1,2,5-benzothiadiazepines*

Tetracyclic benzothiadiazepines (**72**) were synthesised as analogues of the antidepressant aptazapine by treatment of the precursor *N*5-substituted pyrrolobenzothiadiazepine (**71**) (Scheme 22) with lithium aluminium hydride,[18] a process that proceeds *via* a cyclisation and double amide reduction. The precursor (**71**) was accessed in turn by reacting the unsubstituted pyrrolobenzothiadiazepine (**70**) with bromoacetylbromide followed by treatment with benzylamine.[18]

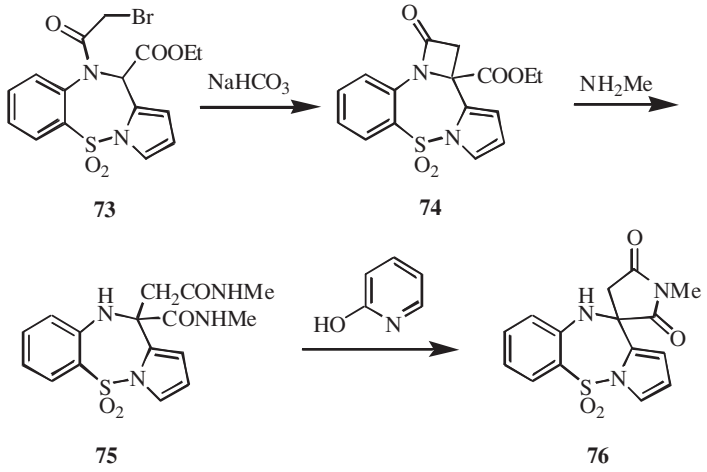
The reaction of compound (**70**) with bromoacetylbromide and isolation of the intermediate α-bromocarbonyl (**73**) (Scheme 23) allowed access to the tetracyclic β-lactam derivative (**74**) after cyclisation mediated by sodium hydrogen carbonate. Opening of the β-lactam ring with methylamine allowed the synthesis of the *bis*-amide derivative (**75**) which underwent ring closure in the presence of 2-hydroxypyridine to form the spiro pyrrolobenzothiadiazepine derivative (**76**).[34]

The conversion of the pyrrolobenzothiadiazepine (**29**) into the imidazolo-fused tetracyclic system (**77**) has been achieved (Scheme 24)[21] *via* the cycloaddition of tosylmethyl isocyanide (TosMIC) to the imine double bond in the presence of butyllithium. The same tetracycle (**77**) could also be accessed by manganese dioxide oxidation of the dihydroimidazole (**80**), which was in turn obtained from the treatment of the aminomethyl derivative (**79**) with triethyl orthoformate. The aminomethyl derivative (**79**) was obtained from the reaction of pyrrolobenzothiadiazepine (**29**) with nitromethane and subsequent Raney nickel reduction of the nitro compound (**78**) (Scheme 24).

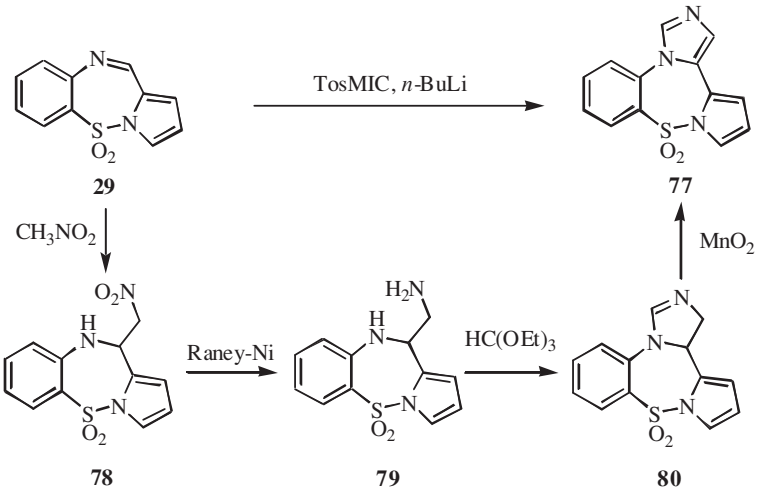
The imidazo fused 1,2,5-benzothiadiazepine TIBO analogues (**8**) were constructed from the 1,2,5-benzothiadiazepin-4-one (**81**) as shown in Scheme 25 using a triphosgene based imidazole ring construction methodology. Nitration of 1,2,5-benzothiadiazepin-4-one (**81**) was achieved in 15 % yield. Reduction of the amide was achieved in quantitative yield and was necessary in order to enable the subsequent reaction with triphosgene to occur. Thionation with Lawesson's reagent gave the desired imidazo[1,5,4-ef] fused system (**8**).[16]

The annelation of the pyrrolobenzothiadiazepine nucleus to give the 1,2,4-triazole fused system (**83**) has been achieved[19] (Scheme 26) by the reaction of the parent pyrrolo[2,1-c][1,2,5]benzothiadiazepinone (**43**) (X=Y=H; obtained as shown in Scheme 12) with *di*-morpholinylphosphinic chloride in the presence of sodium hydride, followed by cyclisation of the resultant phosphinyloxyimine (**82**) by reaction with formylhydrazine.

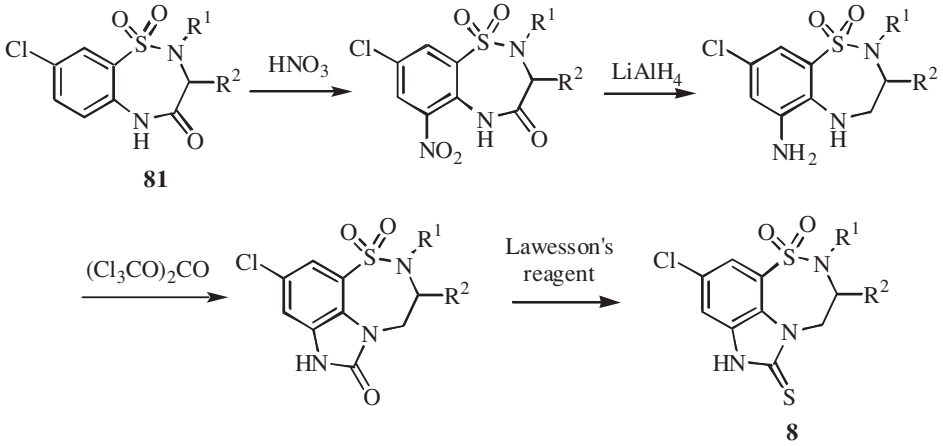
The 4-methoxy-1,2,5-benzothiadiazepine 1,1-dioxides (**66**, R = Me or H) underwent loss of methanol (Scheme 27) on heating in benzene to yield the 2,3-dihydro-1,2,5-benzothiadiazepine 1,1-dioxides (**84**) in over 90 % yield,[33] whereas base induced elimination of ethanol from the 3-ethoxy derivative (**15**) gave the 3,4-dihydro-1,2,5-benzothiadiazepine (**85**).[20] The reduction of compound (**84**) with $LiAlH_4$ or the reaction of compound (**66**) with $NaBH_4$ each resulted in the isolation of the reduced compound (**86**) in high yield (Scheme 27).[33]



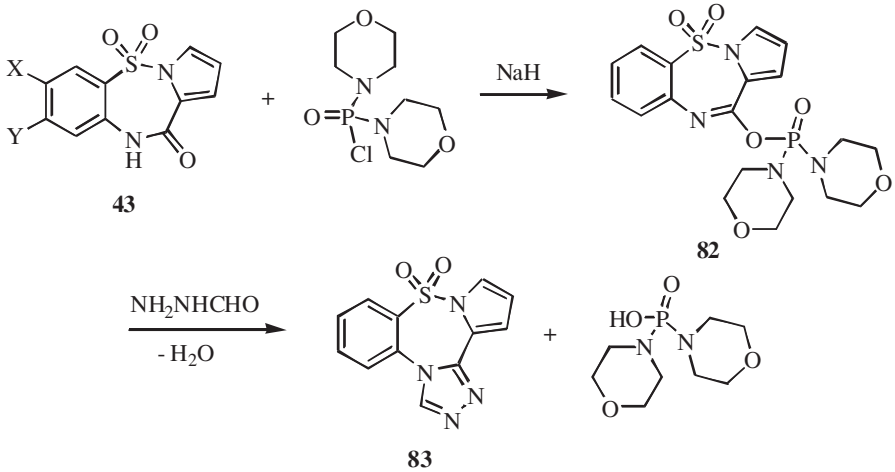
Scheme 23



Scheme 24

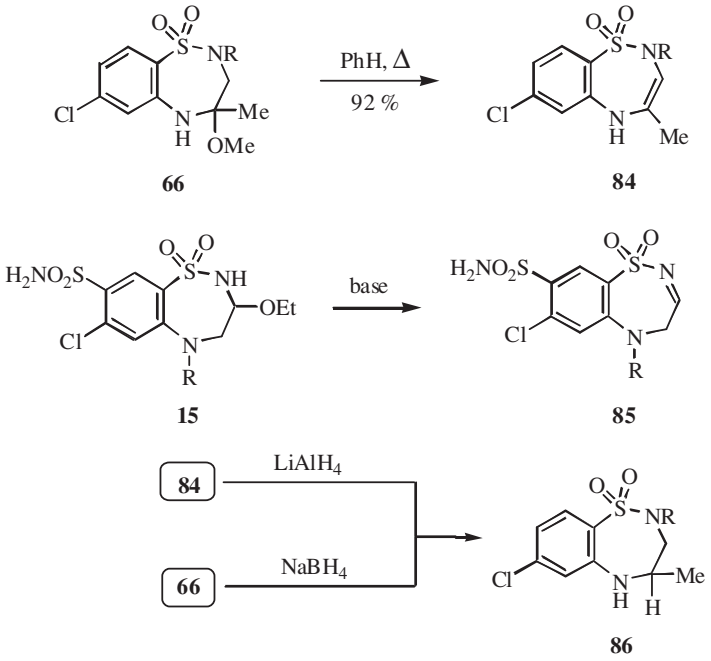


Scheme 25

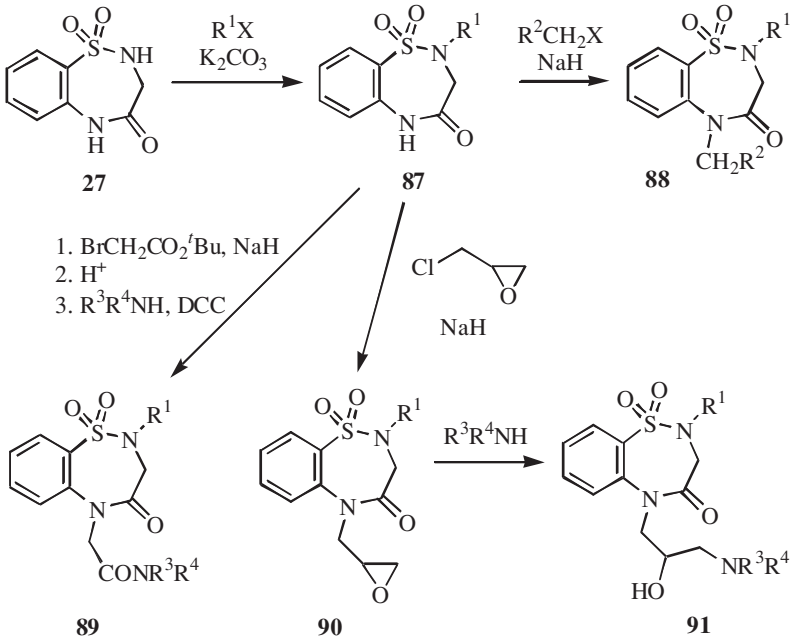


Scheme 26

Work done by Ogawa and Matsushita[6] on the parent 1,2,5-benzothiadiazepin-4-one 1,1-dioxide (**27**) offers a useful insight into the reactivity of the two different nitrogen atoms that are present in this system. Thus, as shown in Scheme 28, treatment with a primary alkyl halide in the presence of sodium carbonate gave the 2-alkyl substituted derivatives (**87**). Reaction of these with a second primary alkyl halide in the presence of sodium hydride gave the *N*,*N*-dialkyl derivatives (**88**). Reaction of 1,2,5-benzothiadiazepin-4-one 1,1-dioxide (**87**) with *tert*-butyl bromoacetate allowed the synthesis of the *tert*-butyl ester which was easily hydrolysed to the carboxylic acid and hence converted into a range of amides (**89**), many of which exhibited antiarrhythmic activity. Substitution at the 4-position was also possible with epichlorohydrin which afforded the epoxypropyl derivatives (**90**). The amino hydroxypropyl derivatives (**91**) were obtained after reaction of the epoxypropyl derivatives (**90**) with an amine, although these latter showed no antiarrhythmic activity.



Scheme 27



Scheme 28

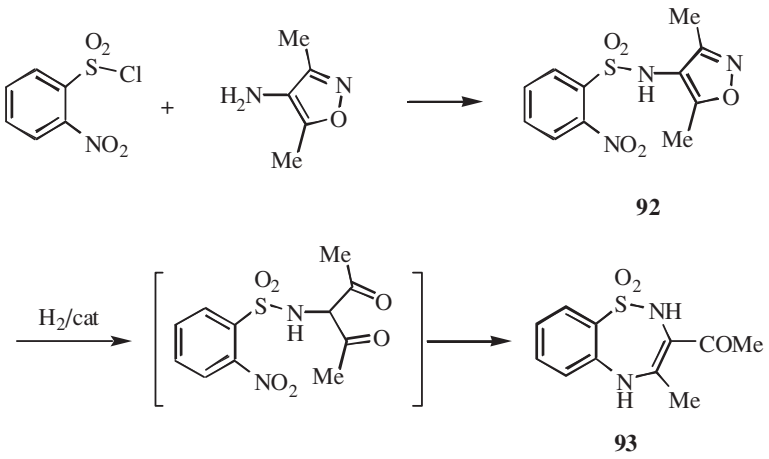
2.8 *Synthesis by other methods*

The reaction of 2-nitrobenzenesulfonyl chloride with 4-amino-3,5-dimethylisoxazole, shown in Scheme 29, yields the isoxazole (**92**), which on catalytic hydrogenation underwent a reductive ring opening of the isoxazole, reduction of the nitro group and a final cyclisation to give the 1,2,5-benzothiadiazepine (**93**).[4a]

Several of the methods that are used to access the pyrrolobenzothiadiazepines, some touched upon above, rely upon the construction of the 3,4 C–C and 4,5 C–N simultaneously. Thus, the reaction of 1-(2-aminobenzenesulfonyl)pyrrole (**16**) with alkyl 3,3-dimethoxypropionates in aqueous acetic acid furnished alkyl-10,11-dihydropyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-11-acetate 5,5-dioxides (**94**), whilst the reaction with ethyl glyoxylate hemiacetal afforded the pyrrolo-benzothiadiazepine (**95**) in high yield (94 %) (Scheme 30).[1,14] Reaction of an acid chloride with 1-(2-aminobenzenesulfonyl) pyrrole (**16**) followed by phosphorus oxychloride mediated Bischler-Napieralski type ring closure gave ready access to the pyrrolobenzothiadiazepines (**96**),[17] whilst treatment with triphosgene has been used to provide access to the pyrrolobenzothiadiazepinones (**97**).[14,35]

3. Conclusions and outlook

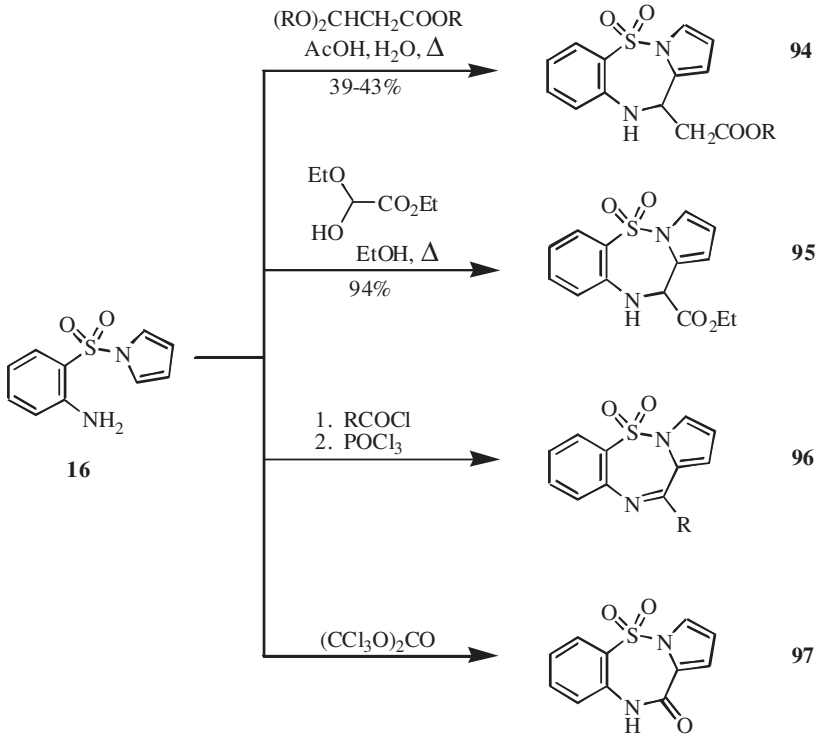
The structural similarity of the 1,2,5-benzothiadiazepine 1,1-dioxides to the 'privileged'[36] 1,4-benzodiazepine pharmacophore will ensure that approaches to 1,2,5-benzothiadiazepine 1,1-dioxides will continue to flourish as a means of providing further analogues of the 1,4-benzodiazepines. Moreover,



92

93

Scheme 29



16

94

95

96

97

Scheme 30

the emerging usefulness of the 1,2,5-benzothiadiazepine 1,1-dioxides as targets in their own right should ensure a productive future in the areas of synthesis and medicinal chemistry with, for example, promising activities as inhibitors of proteinases and metalloproteinases, as non-nucleosidic reverse transcriptase inhibitors, as TACE inhibitors, and as anti-tumour compounds in general. Fused tricyclic and tetracyclic 1,2,5-benzothiadiazepines, such as the tricyclic pyrrolobenzothiadiazepines, are showing particular, but not exclusive, promise in these areas. Key areas which may begin to attract attention, particularly as new biological activities are discovered, are those involving polymer supported, automated or combinatorial approaches, areas that are, surprisingly, yet to emerge for these compounds.

References

1 T. Tsuchiya, in *Comprehensive Heterocyclic Chemistry II – A Review of The Literature 1982–1995*; A.R. Katritzky, C.W. Rees and E.F.V. Scriven (Eds.); Pergamon: New York, 1996; Vol. 9: *Seven-membered & larger rings & fused derivatives*; G.R. Newkome (Vol. Ed.); Chapter 9.15: *Seven-membered rings with three-heteroatoms 1,2,5*; pp. 344.

2 K. Hemming, in *Second Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds*; M. Sainsbury (Ed.); Elsevier Science: Amsterdam, 1999; Vol. IVK, Chap. 52: *Compounds with larger heterocyclic rings: seven-membered ring compounds with two or more different elements in the ring*, pp. 288.

3 J.T. Sharp, in *Comprehensive Heterocyclic Chemistry*; A.R. Katritzky and C.W. Rees (Eds.); Pergamon: New York, 1984; Vol. 7: *Small & Large Rings*; W. Lwowski, (Vol. Ed.); Chapter 5.18: *Seven-membered rings with two or more heteroatoms*, pp. 644.

4 (a) O. Migliara, S. Petruso and V. Spiro, *J. Heterocycl. Chem.*, 1979, **16**, 835; (b) P.H.L. Wei and S.C. Bell, US patent 3453266 (1969); Chemical Abstracts, **71**: 91553.

5 I. Starke, M.U.J. Dahlstrom, D. Blomberg, S. Alenfalk, T. Skjaret and M. Lemurell, World patent WO 2003022286 (2003); Chem. Abs., **138**: 238208.

6 K. Ogawa and Y. Matsushita, *Chem. Pharm. Bull.*, 1992, **40**, 2442.

7 K. Leftheris, J.T. Hunt and C.Z. Ding, US patent 6156746 (2000); Chem. Abs., **134**: 29439.

8 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 and C.P. Decicco, *J. Med. Chem*., 2003, **46**, 1811.

9 T.M. Krülle and J.C.H.M. Wijkmans, *Tetrahedron*, 2001, **57**, 7021.

10 (a) F. Borsini, G. Volterra, A. Lecci, S. Evangelista, A. Mancinelli, C. Cutrufo, M. Parlini, T. Mennini, D. Barone and A. Meli, *Arzneim. Forsch. Drug Res*., 1991, **41**-**1**, 573–580; (b) D. Giannotti, G. Viti, P. Sbraci, V. Pestellini, G. Volterra, F. Borsini, A. Meli, P. Dapporto and P. Paoli, *J. Med. Chem.,* 1991, **34**, 1356

11 (a) D. Bellarosa, G. Antonelli, F. Bambacioni, D. Giannotti, G. Viti, R. Nannicini, A. Giachetti, F. Dianzani, M. Witvrouw, R. Pauwels, J. Desmyter and E. De Clercq, *Antiviral Res*., 1996, **30**, 109; (b) D. Giannotti, G. Viti, R. Nannicini, V. Pestellini and D. Bellarosa, *Bioorg. Med. Chem. Lett*., 1995, **5**, 1461.

12 R. Di Santo, R. Costi, M. Artico, S. Massa, M. E. Marongiu, A. G. Loi, A. De Montis and P. La Colla, *Antiviral Chem. Chemother.*, 1998, **9**, 127.

13 M. Artico, R. Silvestri, E. Pagnozzi, G. Stefancich, S. Massa, A. G. Loi, M. Putzolu, S. Corrias, M. G. Spiga and P. La Colla, *Bioorg. Med. Chem*., 1996, **4**, 837.

14 R. Silvestri, M. Artico, E. Pagnozzi, G. Stefancich, S. Massa, P. La Colla, A. G. Loi, M. G. Spiga, S. Corrias and D. Lichino, *Farmaco*, 1996, **51**, 425.

15 (a) J. Adams and V.J. Merluzzi, in *The Search For Antiviral Drugs-Case Histories From Concept To Clinic*; J. Adams and V.J. Merluzzi (Eds.); Birkhäuser: Boston, 1993; Chapter 3: *Discovery of nevirapine, a non-nucleoside inhibitor of HIV-1 reverse transcriptase*, pp. 45. (b) V.J. Merluzzi, K.D. Hargrave, M. Labadia, K. Grozinger, M. Skoog, J.C. Wu, C.-K. Shih, K. Eckner, S. Hattox, J. Adams, A.S. Rosenthal, R. Faanes, R.J. Eckner, R.A. Koup and J.L. Sullivan, *Science*, 1990, **250**, 1411.

16 R. Costi, R. Di Santo, M. Artico and S. Massa, *J. Heterocycl. Chem*., 2002, **39**, 81.

17 F. Chimenti, S. Vomero, V. Nacci, M. Scalzo, R. Giuliano and M. Artico, *Farmaco (Ed. Sci.)*, 1974, **29**, 589

18 G. Stefancich, R. Silvestri, E. Pagnozzi and M. Artico, *J. Heterocycl. Chem*., 1994, **31**, 867.

19 M. Artico, R. Silvestri and G. Stefancich, *Synth. Commun*., 1992, **22**, 1433.

20 C.W. Whitehead and J.J. Traverso, *J. Org. Chem*., 1963, **28**, 743.

21 R. Silvestri, M. Artico, E. Pagnozzi and G. Stefancich, *J. Heterocycl. Chem*., 1994, **31**, 1033.

22 K. Hemming and N. Patel, *Tetrahedron Lett*., 2004, **45**, 7553 – 7556.

23 Y.G. Gololobov and L.F. Kasukhin, *Tetrahedron*, 1992, **48**, 1353.

24 K. Hemming and C. Loukou, *Tetrahedron*, 2004, **60**, 3349.

25 R. Di Santo, R. Costi, M. Artico and S. Massa, *J. Heterocycl. Chem*., 1996, **33**, 2019.

26 N. Langlois and R.Z. Andriamialisoa, *Heterocycles*, 1989, **29**, 1529.

27 D.E. Thurston and D.S. Bose, *Chem. Rev.*, 1994, **94**, 433.

28 R. Silvestri, A. Pifferi, G. De Martino, S. Massa, C. Saturnino, M. Artico, *Heterocycles*, 2000, **53**, 2163.

29 C. Loukou, PhD. Thesis, University of Huddersfield, UK, 2004, Chapter 3.

30 (a) S. Eguchi, K. Yamashita, Y. Matsushita and A. Kakehi, *J. Org. Chem*., 1995, **60**, 4006; (b) P. Molina, I. Díaz and A. Tárraga, *Tetrahedron*, 1995, **51**, 5617; (c) I. A. O'Neil, C.L. Murray, R.C. Hunter, S. B. Kalindjian and T.C. Jenkins, *Synlett*, 1997, 75.

31 B. Anwar, P. Grimsey, K. Hemming, M. Krajniewski and C. Loukou, *Tetrahedron Lett*., 2000, **41**, 10107.

32 S.M. Weinreb, *Acc. Chem. Res*., 1988, **21**, 313.

33 G.F. Field, W.J. Zally and L.H. Sternbach, *J. Org. Chem*., 1971, **36**, 2968.

34 R. Silvestri, E. Pagnozzi, G. Stefancich and M. Artico, *Synth. Commun*., 1994, **24**, 2685.

35 R. Di Santo, R. Costi, M. Artico and S. Massa, *Farmaco*, 1997, **52**, 375.

36 (a) B.E. Evans, K.E. Rittle, M.G. Bock, R.M. DiPardo, R.M. Freidinger, W.L. Whitter, G.F. Lundell, D.F. Veber, P.S. Anderson, R.S.L. Chang, V.J. Lotti, D.J. Cerino, T.B. Chen, P.J. Kling, K.A. Kunkel, J.P. Springer and J. Hirschfield, *J. Med. Chem.,* 1988, **31**, 2235; (b) A.A. Patchett and R.P. Nargund, *Ann. Rep. Med. Chem.,* 2000, **35**, 289; (c) S. Herrero, M.T. García-López and R. Herranz, *J. Org. Chem.,* 2003, **68**, 4582.