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Synthesis, Conformation and Antiproliferative Activity of Isothiazoloisoaxazole 1,1-dioxides


Sixteen new isothiazoloisoaxazole 1,1-dioxides, one new isothiazolotriazole and one new isothiazolopyrazole have been synthesised by using 1,3-dipolar cycloadditions to isothiazole 1,1-dioxides. One sub-set of these isothiazoloisoaxazoles showed low μM activity against a human breast carcinoma cell line, whilst a second sub-set plus the isothiazolotriazole demonstrated an interesting restricted rotation of sterically hindered bridgehead substituents. A thiazete 1,1-dioxide produced from one of the isothiazole 1,1-dioxides underwent conversion into an unknown 1,2,3-oxathiazolin-2-oxide upon treatment with Lewis acids, but was inert towards 1,3-dipoles and cyclopropenones. Six supporting crystal structures are included.

Introduction

Four-membered heterocyclic rings containing one nitrogen atom are well known within organic chemistry. The field is dominated by the β-lactams (1) [Figure 1] due to the importance that they have acquired as anti-infective agents. The corresponding β-sultams (2) are also known and have attracted attention as taurine precursors, β-lactamase inhibitors, D,D-peptidase inhibitors, human neutrophil elastase inhibitors, azoreductase inhibitors, anti-inflammatory agents, potential treatments for alcohol dependency, SPase I inhibitors and ClpP protease inhibitors, and have attracted other mechanistic and synthetic efforts. β-Sultam chemistry been a focus of our research for some time.

Figure 1. Heterocycles of interest in this work

Our interest in four-membered ring nitrogen heterocycles has also included the study of the chemistry of the unsaturated 1-azetine (3), a system that is easily accessed from β-lactams, although the 1-azetine remains a heterocycle that attracts very little attention. Nonetheless, we have shown that 1-azetines are able to act as precursors for the synthesis of benzoisoquinolines, homotropane related heterocycles and pyridines via a formal [3+2]-cycloaddition reaction with cyclopropenones (which act as all-carbon 1,3-dipole equivalents) as well as acting as dipolarophiles for the synthesis of 1,2,4-oxadiazoles via reaction with nitrite oxides. As a result of these successes, and given our interest in the β-sultam nucleus, we wished to explore the chemistry of the unsaturated β-sultam system, the thiazete 1,1-dioxide (4). In parallel with our studies on the 1-azetine heterocycle, we anticipated that the thiazete 1,1-dioxide nucleus would be a suitable precursor for cyclopropenone based [3+2]-cycloaddition processes and 1,3-dipolar cycloadditions, thus providing access to novel bicyclic β-sultams. We were particularly attracted to the thiazete 1,1-dioxide (5a) that was produced by Clerici and co-workers via ring contraction of an isothiazole 1,1-dioxide (6a) and by the under-explored and appealing nature of the chemistry that leads to this 4-membered unsaturated heterocycle.

Results and discussion

Synthesis and Reactivity of Isothiazole 1,1-dioxides and Thiazete 1,1-dioxides

We synthesised the thiazete 1,1-dioxide (5a) from the precursor isothiazole 1,1-dioxide (6a) by adapting the route described by Clerici as shown in Scheme 1. Thus, dibromination of an enone precursor gave a mixture of dibromo compounds (7a, Ar = 4-MeOC₆H₄) which was reacted with...
diethylamine to give intermediate (8a, Ar = 4-MeOC₆H₄, R = Et, 81% yield) as an isolable, adequately characterised but, in our hands, rapidly degrading intermediate.

Treatment of compound (8a) with methanesulfonyl azide initiates a reaction whereupon the alkene undergoes a 1,3-dipolar cycloaddition followed by loss of phenyl diazomethane to give an 82% yield of the pure N-methanesulfonylamidine (9a, Ar = 4-MeOC₆H₄, R = Et). Cyclisation of compound (9a) with t-butoxide in THF gave the alcohol (10a, Ar = 4-MeOC₆H₄, R = Et, 89%). The alcohol was converted into the corresponding tertiary chloride (11a) which formed in 95% yield together with 4% of the dichloro compound (12a). Elimination of HCl from compound (11a) gave an 86% yield of the isothiazole 1,1-dioxide (13a, Ar = 4-MeOC₆H₄, R = Et), whilst elimination of HCl from the dichloro compound 12a gave the 5-chloroisothiazole 1,1-dioxide (14a). The isothiazole 1,1-dioxide (13a) was converted (93% yield) into the 5-bromoisothiazole 1,1-dioxide (15a) and thence to the 5-methanesulfonylisothiazole 1,1-dioxide (16a, Ar = 4-MeOC₆H₄, R = Et) via the 5-methanesulfonyl derivative (16a) into the methanesulfonyl derivative (16a) but never reached the 97% yield achieved with the bromo derivative (15a). Direct oxidation of compound (16a) into (6a) was also found to be convenient, albeit in a reduced single step yield of 51%. When 5-methanesulfonyl-isothiazole 1,1-dioxide (6a) was treated with sodium azide in acetonitrile it underwent the expected but remarkable ring contraction (see later for a mechanistic discussion) to furnish the desired thiazete 1,1-dioxide (5a, Ar = Ar = 4-MeOC₆H₄, R = Et).

We attempted the reaction of the thiazete 1,1-dioxide (5a) with nitriles and cyclopropenones (19) in order to form cycloaducts (18) and (20), illustrated in Scheme 1. No reactions of the imine present in the thiazete 1,1-dioxide (5a) were observed, and the starting material was returned unchanged in all cases, a huge disappointment given that we had shown that the imine within the 1-azetine system reacts easily with both nitrile oxides and cyclopropenones.21-24 Other 1,3-dipoles (nitrile ylides, nitrilimines, nitrones, aryl azides and azomethine ylides) and dienes were found to be similarly unreactive. Interestingly, when the cyclopropenone reaction was attempted in the presence of a Lewis acid, a reaction was observed. On these occasions, the product was found to be the previously unreported 1,2,3-oxathiazolin-2-oxide (21) – see Scheme 1, the product of a hitherto unknown rearrangement of the thiazete 1,1-dioxide (5a). This product was also obtained in the absence of the cyclopropenone. Compound (21) was typically formed as a ~2.5:1 mixture of diastereoisomers with the major diastereoisomer isolated in a maximum yield of 31% while using zinc chloride as the Lewis acid, and for which we were unable to determine the relative stereochemistry. A possible mechanism for the formation of compound (21) from (5a) is shown in Scheme 2, based upon a known rearrangement of simple (saturated) 3-aryl β-sultams into simple (saturated) 1,2,3-oxathiazolidines.29

![Scheme 1. Synthesis and reactivity of thiazete 1,1-dioxide (5)](image)

Disappointed by the inert nature of thiazete 1,1-dioxide (5a) towards 1,3-dipoles and cyclopropenones, we next investigated the reactivity of isothiazole 1,1-dioxides (10a – 17a) and (6a, Ar = 4-MeOC₆H₄, R = Et). No reactivity was observed from any of these compounds towards cyclopropenones. Compounds (10a – 12a) were also unreactive towards 1,3-dipoles. However, compounds (13a – 15a), (17a) and (6a) [Ar = 4-
MeOC₆H₄, R = Et] were reactive towards a series of five nitrile oxides, forming a series of isothiazoloisoxazoles (22) as shown in Scheme 3 and Table 1 (entries a – i). It is of note that we found the thioether compound (16a) (entry j, Table 1) to be unreactive, possibly due to the electron donating nature of this substituent when compared to the other isothiazole 1,1-dioxides used. The reactivity of compound (13a) towards nitrile oxides has also been investigated by Clerici (see below).³⁰

It is of note that all of the reactions were regioselective and diastereoselective, giving the syn-diastereoisomer shown in Scheme 3. The observed regiochemistry is predictable on the basis of the alkene polarity and was apparent from HMBC spectra. The syn-diastereoselectivity is explained by the concerted nature of the cycloaddition. The stereochemistry was apparent from NOESY spectra and other NMR studies (see below). We were also able to confirm the structures of compounds (22a), (22b) [both diastereoisomers] and (22i) by X-ray crystallographic studies.³¹

We next decided to extend the scope of this reaction and produced a range of five additional isothiazole 1,1-dioxides (13b - f) (as shown in Table 2), four of which (13b, c, d and f) are previously unreported and were produced using the route described in Scheme 1 in the yields shown in Table 2. In general, the chemistry proceeded without incident. However, all attempts to obtain pure samples of intermediate (8b - f) were unsuccessful. Fortunately, we found that the crude mixtures could be treated with methanesulfonyl azide whereupon the pure N-methanesulfonylamidines (9b - f) could be isolated in reasonable yields (see Table 2). There is great interest in azide to alkene 1,3-dipolar cycloaddition chemistry,³²-³⁷ so we were particularly pleased to see that the key 1,3-dipolar cycloaddition/1,3-dipolar cycloreversion based conversion of compounds (8b - f) into (9b - f) showed itself to be repeatable and reliable even with crude starting material. Conversion of compounds (9b - f) into heterocycles (13b - f, see Table 2 for Ar and R) proceeded without further issues. Isothiazole 1,1-dioxides (13b - f) were reacted with nitrile oxides to give the isothiazoloisoxazoles (22k - t), again as single regio- and syn-diastereoisomers, as shown in Table 1.

It is important to note that Clerici and co-workers have reported the synthesis of a library of six isothiazoloisoxazoles accessed from one of these isothiazole 1,1-dioxides (13a, Ar = 4-MeOC₆H₄, R = Et)³⁰ and six nitrile oxides as well as two further adducts isolated from the reactions of 3-benzylamino-isothiazole 1,1-dioxide³⁸ (not studied in our work). However, only 3 of the 19 compounds reported in Table 1 (compounds 22a, 22d and 22e) have been reported previously, and our work has demonstrated that this chemistry is more widely applicable than reported previously, both in terms of precursor (13) synthesis and adducts (22) produced.

![Scheme 3. Synthesis of isothiazoloisoxazoles (22) [see Table 1]](image)

### Table 1. Scope of isothiazoloisoxazole structures (22) [see Scheme 3]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Y</th>
<th>R</th>
<th>R₁</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22a</td>
<td>4-MeOC₆H₄</td>
<td>H</td>
<td>Et</td>
<td>CO₂Et</td>
<td>86</td>
</tr>
<tr>
<td>22b</td>
<td>4-MeOC₆H₄</td>
<td>H</td>
<td>Et</td>
<td>C₆H₅</td>
<td>71</td>
</tr>
<tr>
<td>22c</td>
<td>4-MeOC₆H₄</td>
<td>H</td>
<td>Et</td>
<td>2-N,C₆H₄</td>
<td>62</td>
</tr>
<tr>
<td>22d</td>
<td>4-MeOC₆H₄</td>
<td>H</td>
<td>Et</td>
<td>4-NO₂C₆H₄</td>
<td>42</td>
</tr>
<tr>
<td>22e</td>
<td>4-MeOC₆H₄</td>
<td>H</td>
<td>Et</td>
<td>4-MeOC₆H₄</td>
<td>71</td>
</tr>
<tr>
<td>22f</td>
<td>4-MeOC₆H₄</td>
<td>Cl</td>
<td>Et</td>
<td>4-MeOC₆H₄</td>
<td>56</td>
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<tr>
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<td>4-MeOC₆H₄</td>
<td>Br</td>
<td>Et</td>
<td>4-MeOC₆H₄</td>
<td>54</td>
</tr>
<tr>
<td>22h</td>
<td>4-MeOC₆H₄</td>
<td>SOMe</td>
<td>Et</td>
<td>4-MeOC₆H₄</td>
<td>52</td>
</tr>
<tr>
<td>22i</td>
<td>4-MeOC₆H₄</td>
<td>SOMe</td>
<td>Et</td>
<td>4-MeOC₆H₄</td>
<td>68</td>
</tr>
<tr>
<td>22j</td>
<td>4-MeOC₆H₄</td>
<td>SMe</td>
<td>Et</td>
<td>4-MeOC₆H₄</td>
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<td>4-MeOC₆H₄</td>
<td>H</td>
<td>n-Pr</td>
<td>4-MeOC₆H₄</td>
<td>29</td>
</tr>
<tr>
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<td>H</td>
<td>n-Pr</td>
<td>4-ClC₆H₄</td>
<td>30</td>
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<tr>
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<td>H</td>
<td>Et</td>
<td>4-ClC₆H₄</td>
<td>51</td>
</tr>
<tr>
<td>22n</td>
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<td>H</td>
<td>Et</td>
<td>4-MeOC₆H₄</td>
<td>45</td>
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<td>H</td>
<td>n-Pr</td>
<td>4-MeOC₆H₄</td>
<td>25</td>
</tr>
<tr>
<td>22p</td>
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<td>H</td>
<td>n-Pr</td>
<td>4-ClC₆H₄</td>
<td>29</td>
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<tr>
<td>22q</td>
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<td>Et</td>
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<td>39</td>
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<tr>
<td>22r</td>
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<td>H</td>
<td>Et</td>
<td>4-ClC₆H₄</td>
<td>41</td>
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<td>22s</td>
<td>4-MeC₆H₄</td>
<td>(CH₃)s</td>
<td>Et</td>
<td>4-MeOC₆H₄</td>
<td>54</td>
</tr>
<tr>
<td>22t</td>
<td>4-MeC₆H₄</td>
<td>(CH₃)s</td>
<td>Et</td>
<td>4-ClC₆H₄</td>
<td>28</td>
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</tbody>
</table>

### Table 2. Range of isothiazole 1,1-dioxides (13) [see Scheme 1]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>Yield (13) (%)</th>
<th>Yield (11) (%)</th>
<th>Yield (10) (%)</th>
<th>Yield (9) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td>4-MeOC₆H₄</td>
<td>n-Pr</td>
<td>76</td>
<td>97</td>
<td>99</td>
<td>80</td>
</tr>
<tr>
<td>c</td>
<td>4-ClC₆H₄</td>
<td>Et</td>
<td>79</td>
<td>82</td>
<td>83</td>
<td>53</td>
</tr>
<tr>
<td>d</td>
<td>4-ClC₆H₄</td>
<td>n-Pr</td>
<td>97</td>
<td>85</td>
<td>76</td>
<td>75</td>
</tr>
<tr>
<td>e</td>
<td>4-MeC₆H₄</td>
<td>Et</td>
<td>30</td>
<td>66</td>
<td>77</td>
<td>29</td>
</tr>
<tr>
<td>f</td>
<td>4-MeC₆H₄</td>
<td>(CH₃)s</td>
<td>62</td>
<td>71</td>
<td>42</td>
<td>54</td>
</tr>
</tbody>
</table>

Given that compound (6a) underwent the ring contraction to give thiazete (5a) upon treatment with sodium azide, we also explored the reactivity of compounds (14a – 17a, Ar = 4-MeOC₆H₄, R = Et) towards sodium azide. Only compound (17a) showed a reaction and in this case we were able to isolate the previously unreported isothiazolotriazole cycloadducts (23a and b) [Scheme 4] as a ~5:6 mixture of diastereoisomers in a combined yield of 49% [we confirmed the structure of the major diastereoisomer by X-ray crystallography]. Clerici and co-workers also isolated an isothiazolotriazole when exploring the reactivity of isothiazole 1,1-dioxide (13a, Ar = 4-MeOC₆H₄, R = Et) towards sodium azide. Together, these observations suggest that the ring contraction mechanism for the addition of sodium azide to isothiazole 1,1-dioxide (6a) to give the thiazete 1,1-dioxide (5a) may proceed via an isothiazolotriazole
intermediate (as shown in Scheme 4) which, in the case of the sulfone, collapses to give the ring-contracted final product due to enhanced stability of the sulfone leaving group versus the sulfoxide leaving group. Finally, also shown in Scheme 4, we reacted the isothiazole 1,1-dioxide (13a) with a nitrilimine to give adduct (24, Ar = 4-MeOC6H4, R = Et) in 41% yield, a structure that we confirmed by X-ray crystallographic studies.31 Attempted reaction with other nitrilium betaines (nitrile ylides and nitrile sulfides) was not fruitful, although adducts of isothiazole 1,1-dioxide (13a) with Münchnones, diazo compounds and aryl azides have been reported.40-42

![Scheme 4. Synthesis of azide and nitrilimine adducts (23) and (24) [Ar = 4-MeOC6H4, R = Et]](image)

**Conformational Studies of Isothiazoloisoxazoles**

The NMR spectra of the previously unreported cycloadducts (22f-i, Figure 2) revealed some unexpected results. For compounds (22f) and (22g), the two pairs of aromatic protons on the bridgehead aryl group were expected to give two doublets in the 1H NMR spectra integrating to two protons each. Instead, these protons appeared as two broad signals in a 1:3 ratio, indicating that they are in different electronic environments due, we assume, to a restricted rotation of the aromatic ring on the ring junction.

For compound (22h), formed as a separable mixture of diastereoisomers, the aromatic protons of the bridgehead aryl group appeared as four distinct (albeit overlapping) signals which were broad for one isomer but resolved for the other. For compound (22i) the broadening of the signals in the 1H NMR spectrum disappeared and the four aromatic protons of the bridgehead aryl group gave four very distinctive doublets of doublets. These results also indicate a restricted rotation of the aromatic ring and a different electronic environment for each proton.

In the 13C NMR spectra for compounds (22f) and (22g), two flattened but distinct peaks appeared for the two aromatic CH carbons closer to the stereogenic centre at the ring junction, whereas no discrimination was observed between the two other aromatic CH carbons, *i.e.* those *ortho* to the methoxy group on the bridgehead aryl group. For the two diastereoisomers of compound (22h) and for compound (22i), the four aromatic CH carbons on the ring junction aryl group appeared as separate signals. These observations again indicate that the aromatic CH carbons on the ring junction aryl group are in different environments, providing further evidence of the restriction of the rotation of the aromatic ring. Steric hindrance between the bridgehead aryl group and the substituent Y across a *syn-*ring junction as shown in Figure 2 would account for the restricted rotation of the aromatic ring.

![Figure 2 Restricted rotation of the bridgehead aryl group](image)

The broadening of the signals for the aromatic protons in the 1H NMR spectra decreases in the order Cl < Br < SOMe < SO2Me. The larger the substituent, the smaller the amplitude of the rotation, which then allows a more defined electronic environment,43 and a more resolved signal. This phenomenon also accounts for the intact AB system that is observed in those examples of adducts (22) where Y = H in which there is free rotation of the aromatic ring at the ring junction due to minimal steric hindrance. In these cases, the two aromatic protons in each proton pair are in the same environment and appear as the expected two doublets.

In the 13C NMR spectra of compounds (22f) and (22g), efficient relaxation and environmental exchange accounts for the observed flattening, broadening and coalescence of some signals.43 For compounds (22h) and (22i), the presence of four aromatic CH carbon signals for the bridgehead aryl group is due to the increasingly restricted rotation of the aromatic ring at the ring junction. In those systems with Y = H, rotation is not restricted and only two CH environments are observed for the bridgehead aryl group.
Compounds (23a/b) – with only one aryl ring – exhibited the same phenomena, with the presence of four CH signals in the aromatic region of the $^{13}$C NMR spectrum for each diastereoisomer and the presence of four non-equivalent aromatic protons (with some overlap) in the $^1$H NMR spectra.

Antiproliferative Activity of Isothiazoloisoxazoles

Whilst the biological activity of monocyclic isothiazole dioxides as protein farnesyltransferase inhibitors$^{44,45}$ and antiproliferatives$^{45,46}$ has been established, we are aware of no reports dealing with bicyclic systems. Thus, we investigated the activity of a subset of the isothiazoloisoxazoles as antiproliferative agents. Compounds (22k), (22m), (22o) and (22p) had suitable solubility in DMSO and were tested for cytotoxicity against human breast carcinoma cell line, MCF-7 cells. IC$_{50}$ values are shown in Table 3. Compound (22o) only showed inhibition of cell growth after 96 hours of incubation whereas compounds (22k), (22m) and (22p) showed inhibition at 48 and 72 hours. Compound (22m) showed the greatest activity, and work is currently underway in our laboratories to discover derivatives with nM levels of activity.

Table 3. IC$_{50}$ values for isothiazoloisoxazoles against MCF-7 cells

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$ µM (48 hr)</th>
<th>IC$_{50}$ µM (72 hr)</th>
<th>IC$_{50}$ µM (96 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22k</td>
<td>8.50</td>
<td>6.25</td>
<td>3.75</td>
</tr>
<tr>
<td>22m</td>
<td>3.10</td>
<td>3.75</td>
<td>1.50</td>
</tr>
<tr>
<td>22o</td>
<td>-</td>
<td>-</td>
<td>5.50</td>
</tr>
<tr>
<td>22p</td>
<td>8.25</td>
<td>5.50</td>
<td>6.50</td>
</tr>
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</table>

Experimental

General Considerations

All reactions were monitored and analysed by TLC using Macherey-Nagel 0.2 mm pre-coated Alugram® N/UV$_{254}$ silica gel or alumina gel plates. Column chromatography was conducted using 60 Å, 70 – 230 mesh, 63 – 200 µm silica gel supplied by Sigma-Aldrich. Petroleum ether (PE) refers to the fraction boiling at 40 – 60 °C. Where necessary, 60 Å, 50 – 200 µm, basic alumina gel was used and was supplied by Acros. Analysis by NMR spectroscopy was achieved using Bruker DPX, Bruker AVIII 400 MHz NMR and Bruker AV500 NMR spectrometers. Analysis by high resolution mass spectrometry was achieved using a Bruker Daltonics microOTOF-Q Mass Spectrometer. Infra-red analysis was achieved using a Nicolet 380 FT-IR spectrometer and samples were run as neat oils or solids. Melting point determinations were made using a Stuart, SMP10 digital melting point apparatus. X-ray crystallographic information is given in the Supplementary Information.

MCF-7 cells, human breast carcinoma cell line (American Type Culture Collection) were grown and maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum at 37 °C, 5% CO$_2$. The cells were plated in 96-well culture plates at a density of 1 x 104 cells/well and allowed to adhere at 37 °C for 24 hours. The following day, various doses of the compounds were added to the cells and further incubated for 24 h, 48 h, 72 h or 96 h. The supernatant was removed and MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added for 4 hours. The ability of cells to form formazan crystals by active mitochondrial respiration was determined by using a Microplate reader after dissolving the crystals in DMSO. Cytotoxicity was expressed as a relative percentage of the absorbance measured at 540 nm in the control and extract-treated cells. Data were determined as the mean ± s.e. mean for 4 separate experiments of 8 readings for each dose.

Compounds 5a and 6a$^{26}$ 8a, 8e, 9a, 9c, 10a, 10e, 11a, 11e, 13a and 13e$^{27}$ 15a, 16a$^{28}$ and 22a, 22d and 22e$^{30}$ have been reported previously, although only compounds 5a, 6a and 15a had full spectroscopic characterisation data (including $^{13}$C NMR data) reported. Thus, full characterisation data and improved procedures for the synthesis of these compounds can be found in the Supporting Information. Other compounds are currently unreported. Representative procedures and data appear below for compounds 8, 9b, 10b, 11b, 13b, 14a, 17a, 21, 22b, 22f – i, 23a/b and 24. Data and procedures for compounds 9c, d and f, 10c, d and f, 11c, d and f, 13c, d and f, 22c and 22k – t are detailed in the Supporting Information.

2-(Alkylamino)-1-aryl-3-phenyl-prop-2-en-1-ones (8b – 8d, 8f)

To the 2,3-dibromo-1-aryl-3-phenyl-propan-1-one (7) (4.5 – 5.0 g, 11.4 – 12.6 mmol) stirring in ethanol (10 – 40 mL) at room temperature under an atmosphere of nitrogen was added the amine (2 equivalents, 22.8 – 25.2 mmol) and the mixture was stirred for 24 hours. After this time sodium ethoxide (1 equivalent, 11.4 – 12.6 mmol) was added and the reaction mixture was stirred for a further 24 hours. Solvents were then removed under reduced pressure and the residues were dissolved in dichloromethane. The solution was filtered to remove sodium bromide and the filtrate was concentrated under reduced pressure. The crude products were taken to the next stage without further purification or analysis.

2-(4-Methoxyphenyl)-N’-methylsulfonyl-2-oxo-N,N-dipropyl-acetamide (9b)

Under an atmosphere of nitrogen, a solution of the 2-(dipropylamino)-1-(4-methoxyphenyl)-3-phenyl-prop-2-en-1-one (8b) crude reaction mass (12.56 mmol based upon 7a, 5.0 g) in ethanol (45 mL) was added to a solution of methanesulfonyl azide (1.79 g, 14.80 mmol) in ethanol (15 mL). The reaction mixture was set to stir at reflux for 24 hours. After this time, solvents were removed under reduced pressure. The crude product was purified by gravity silica column chromatography with a 1:1 petroleum ether:ethyl acetate solvent system to yield the pure product as an orange oil (3.40 g, 80%).

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1H NMR δ (400 MHz, CDCl3): 0.73 (3H, t, J = 7.4 Hz, NCH3CH2CH3); 1.01 (3H, t, J = 7.4 Hz, NCH3CH2CH3); 1.41 – 1.69 (2H, m, NCH3CH2CH3); 1.72 – 1.87 (2H, m, NCH3CH2CH3); 2.96 (3H, s, SO2CH3); 2.98 – 3.10 (2H, m, NCH3CH2CH3); 3.35 – 3.44 (1H, m, NCH3CH2CH3); 3.61 – 3.71 (1H, m, NCH3CH2CH3); 3.89 (3H, s, ArOCH3); 7.00 (2H, d, J = 7.8 Hz, ArH); 7.86 (2H, d, J = 7.8 Hz, ArH).

3C NMR δ (100 MHz, CDCl3): 10.94 (NCH3CH2CH3), 11.47 (NCH3CH2CH3), 19.90 (NCH3CH2CH3), 21.72 (NCH3CH2CH3), 42.60 (SO2CH3), 49.53 (NCH3CH2CH3), 51.36 (NCH3CH2CH3), 55.70 (ArOCH3), 114.57 (Ar), 127.69 (Ar), 131.36 (Ar), 162.68 (Ar), 164.88 (N=C=N), 171.15 (C=O).

IR (cm⁻¹): 1264.7, 1513.5, 1581.8.

Under an atmosphere of nitrogen, thionyl chloride (6.38 mL, 87.90 mmol) was added to 3-(dipropylamino)-4-(4-methoxyphenyl)-1,1-dioxo-5H-isothiazol-4-ol (10b) (1.00 g, 2.93 mmol) and the mixture set to stir at reflux for 24 hours. After this time the excess thionyl chloride was removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 10% w/v aqueous sodium bicarbonate solution. The aqueous layer was removed and extracted with dichloromethane (3 × 25 mL) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by gravity silica column chromatography (2:1 PE:EtOAc) to yield the pure product as a yellow oil (1.06 g, 97%).

1H NMR δ (400 MHz, CDCl3): 0.57 (3H, t, J = 7.4 Hz, NCH3CH2CH3); 0.95 (3H, t, J = 7.4 Hz, NCH3CH2CH3); 1.00 – 1.14 (1H, m, NCH3CH2CH3); 1.45 – 4.60 (1H, m, NCH3CH2CH3); 1.61 – 1.87 (2H, m, CH2NCH2); 2.89 – 3.08 (2H, m, NCH3CH2CH3); 3.35 – 3.44 (1H, m, NCH3CH2CH3); 3.47 – 3.56 (1H, m, NCH3CH2CH3); 3.81 (1H, d, J = 14.6 Hz, SO2CH3); 3.84 (3H, s, ArOCH3); 4.16 (1H, d, J = 14.6 Hz, SO2CH3); 6.95 (2H, d, J = 9.0 Hz, ArH); 7.42 (2H, d, J = 8.9 Hz, ArH).

IR (cm⁻¹): 833.5, 959.6, 1015.8, 1128.7, 1166.9, 1234.5, 1258.9, 1291.2, 1541.6, 1596.4.

micrOTOF-Q MS m/z C16H23N2O5S+Na, calculated 363.1349, observed 363.1348.

4-Chloro-4-(4-methoxyphenyl)-1,1-dioxo-N,N-dipropyl-5H-isothiazol-3-amine (11b)

To 4-chloro-4-(4-methoxyphenyl)-1,1-dioxo-N,N-dipropyl-5H-isothiazol-3-amine (11b) (3.72 g, 10.34 mmol) in dry acetone (50 mL) under an atmosphere of nitrogen, anhydrous potassium carbonate (1.57 g, 11.37 mmol) was added and the reaction mixture set to stir at reflux for 24 hours. After this time the excess potassium carbonate and the solvents removed under reduced pressure. The residues were dissolved in dichloromethane and neutralised with 1M aqueous hydrochloric acid. The aqueous layer was removed and extracted with dichloromethane (3 × 25 mL) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by gravity silica column chromatography (1:9 PE:EtOAc) to yield the pure product as a white solid (2.40 g, 95%).
concentrated under reduced pressure to yield the product as a brown oil (3.30 g, 76%) which was a single spot by TLC and did not need to be purified further.

1H NMR δ (400 MHz, CDCl3): 0.43 (3H, t, J = 7.2 Hz, NCH2CH2CH3); 0.95 (3H, t, J = 7.2 Hz, NCH2CH2CH3); 1.32 – 1.44 (2H, m, NCH2CH2CH3); 1.70 – 1.83 (2H, m, NCH2CH2CH3); 2.98 (2H, t, J = 7.8 Hz, NCH2CH2CH3); 3.52 (2H, t, J = 7.6 Hz, NCH2CH2CH3); 3.85 (3H, s, ArOCH3); 6.97 (2H, d, J = 8.8 Hz, ArH); 7.17 (1H, s, SO2CH3); 7.23 (2H, d, J = 8.8 Hz, ArH).

13C NMR δ (100 MHz, CDCl3): 10.51 (CH3); 11.36 (CH3); 19.98 (CH3); 22.62 (CH3); 51.45 (NCH3); 54.29 (NCH3); 55.49 (ArOCH3); 114.59 (Ar); 123.86 (Ar); 128.70 (Ar); 139.69 (Ar); 143.05 (SO2CH3); 160.57 (C=Ar); 161.31 (N=C=N).

HRMS (m/z) (35Cl): [M + H]⁺ for C14H14ClN2O3S calculated 329.0721 measured 329.0719.

5-Chloro-3-diethylamino-4-(4-methoxyphenyl)isothiazol-1,1-dioxide (14a)

A mixture of 4-chloroisothiazol-1,1-dioxide (11a) and 4,5-dichloroisothiazolin-1,1-dioxide (12a) (3.23 g, ~10/1 mixture estimated by NMR) [see Supporting Information] was dissolved in dry acetone (10 mL) and potassium carbonate (1.35 g, 9.77 mmol) was added in one portion. The mixture was heated at reflux temperature under nitrogen for 8 days. The solvent was removed in vacuo and the residue was dissolved in DCM (15 mL) and neutralised with a 10% aqueous solution of hydrochloric acid. The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic layers were washed with water (2 × 10 mL), dried over Na2SO4 and filtered. The solvent was evaporated under reduced pressure to give the crude product as a sticky orange solid (2.21 g). Purification by gravity silica chromatography (PE/ethyl acetate: 2/1) afforded the isothiazol-1,1-dioxide (13a) (1.24 g, data as per Supporting Information) and the 5-chloroisothiazol-1,1-dioxide (14a) as a yellow solid (0.22 g, m.p. = 123 – 125 °C).

1H NMR δ (500 MHz, CDCl3): 7.20 (2H, d, J = 8.5 Hz, ArH); 7.03 (2H, d, J = 8.5 Hz, ArH); 3.87 (3H, s, OCH3); 3.65 (2H, q, J = 7.1 Hz, NCH2CH3); 3.15 (2H, q, J = 7.1 Hz, NCH2CH3); 1.30 (3H, t, J = 7.1 Hz, NCH2CH3); 0.91 (3H, t, J = 7.1 Hz, NCH2CH3).

13C NMR δ (125 MHz, CDCl3): 160.69 (C=N); 160.42 (C=O); 147.75 (C=O); 132.28 (C=Cl); 129.19 (CH, Ar); 121.89 (CH, Ar); 114.94 (CH, Ar); 55.38 (OCH3); 46.46 (NCH2CH3); 43.72 (NCH2CH3); 14.10 (NCH2CH3); 11.92 (NCH2CH3).

IR νmax (cm⁻¹): 2976, 2840, 1624, 1604, 1564, 1508, 1306, 1248, 1206, 1153, 1024, 884, 830, 802, 770.

MS (m/z): 329.1 ([M + H]⁺).

3-Diethylamino-5-methanesulfonyl-4-(4-methoxyphenyl)isothiazol-1,1-dioxide (17a)

3-Diethylamino-5-methanesulfonyl-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (16a) (500 mg, 1.47 mmol) [see Supporting Information], was dissolved in dry DCM (10 mL) and m-CPBA (253 mg, 1.47 mmol) was added in one portion. The reaction was stirred at room temperature under nitrogen and monitored by thin layer chromatography. Further portions of m-CPBA were added to the mixture to complete the reaction (after 6 hours: 51 mg, 0.30 mmol; after 27 hours: 25 mg, 0.14 mmol; after 50 hours: 25 mg, 0.14 mmol). After 54 hours, the m-chlorobenzoic acid precipitate was filtered off, and the filtrate was washed sequentially with a 20% aqueous NaHCO3 solution (5 mL) and water (2 × 5 mL). The organic layer was separated, dried over anhydrous Na2SO4, and the solvent was removed under reduced pressure to give the crude product as a yellow solid which was purified by gravity silica chromatography (PE/ethyl acetate: gradient elution 2/1, 3/2, 1/1) to yield the product as a yellow solid (350 mg, 67%, m.p. = 167 – 169 °C).

1H NMR δ (500 MHz, CDCl3): 7.41 (1H, bs, ArH); 7.15 (1H, bs, ArH); 7.02 (2H, bs, ArH); 3.87 (3H, s, OCH3); 3.66 (1H, dq, J = 13.6 and 7.1 Hz, NCH2CH3); 3.60 (1H, dq, J = 13.6 and 7.1 Hz, NCH2CH3); 3.16 (3H, s, CH3SO); 3.11 (2H, q, J = 7.1 Hz, NCH2CH3); 1.31 (3H, t, J = 7.1 Hz, NCH2CH3); 0.92 (3H, t, J = 7.1 Hz, NCH2CH3).

13C NMR δ (100 MHz, CDCl3): 161.02 (C=O); 158.54 (C=N); 155.81 (ArC=SOCH3); 141.21 (ArC=SOCH3); 129.72 (CH, Ar); 128.66 (CH, Ar); 120.84 (CH, Ar); 114.91 (CH, Ar); 114.56 (CH, Ar); 55.40 (OCH3); 47.26 (NCH2CH3); 43.75 (NCH2CH3); 38.34 (CH3SO); 14.16 (NCH2CH3); 11.72 (NCH2CH3).

1H NMR δ (500 MHz, DMSO-D6) 7.54 (1H, bd, J = 8.2 Hz, ArH); 7.47 (1H, bd, J = 8.2 Hz, ArH); 7.09 (1H, bd, J = 8.2 Hz, ArH); 7.06 (1H, bd, J = 8.2 Hz, ArH); 3.81 (3H, s, OCH3); 3.53 (2H, bq, J = 7.0 Hz, NCH2CH3); 3.08 (2H, bq, J = 7.0 Hz, NCH2CH3); 3.04 (3H, s, CH3SO); 1.20 (3H, t, J = 7.0 Hz, NCH2CH3); 0.83 (3H, t, J = 7.0 Hz, NCH2CH3).

13C NMR δ (125 MHz, DMSO-D6): 160.29 (C=O); 157.68 (C=N); 154.79 (C=C); 139.89 (C=C); 129.98 (CH, Ar); 129.21 (CH, Ar); 121.33 (C, Ar); 114.47 (CH, Ar); 114.28 (CH, Ar); 55.30 (OCH3); 46.54 (NCH2CH3); 43.40 (NCH2CH3); 38.90 (CH3SO); 13.60 (NCH2CH3); 11.47 (NCH2CH3).

IR νmax (cm⁻¹): 2977, 1601, 1561, 1507, 1443, 1406, 1358, 1290, 1247, 1205, 1146, 1066, 1021, 829, 777, 733, 708.

MS (m/z): 357.1 ([M + H]⁺), 713.2 ([2M + H]⁺), 735.2 ([2M + Na]⁺).

HRMS (m/z): [M + NH4]⁺ for C13H23N2O2S2 calculated 374.1203 measured 374.1198.
1,2,3-Oxathiazolin-2-oxide (21)

3-Diethylamino-1,2-thiazetin-1,1-dioxide (5a) (80 mg, 0.26 mmol) and zinc chloride (260 μL of a 1 M solution in diethyl ether, 0.26 mmol) were dissolved in toluene (2 mL). The whole was stirred under nitrogen and heated at reflux for a further 48 hours. The solvent was removed in vacuo to give the crude product as a dark brown oil which was purified by gravity silica chromatography (hexane/EtOAc: 2/1) to give the product as a pure diastereoisomeric fraction (25 mg, 31%) together with a second fraction as a mixture of diastereoisomers (10 mg, 13%).

Pure diastereoisomer:

1H NMR δ (400 MHz, CDCl3) 7.60 (2H, d, J = 8.9 Hz, ArH), 7.00 (2H, d, J = 8.9 Hz, ArH), 3.85 (3H, s, OCH3), 3.58 (2H, q, J = 7.1 Hz, NCH2CH3), 3.24 (1H, q, J = 7.1 Hz, NCH2CH3), 3.00 (3H, t, J = 7.1 Hz, NCH2CH3), 0.83 (3H, t, J = 7.1 Hz, NCH2CH3).

13C NMR δ (100 MHz, CDCl3) 164.72 (Et3N-C=O), 161.23 (C-OMe), 128.81 (CH, Ar), 125.25 (C, Ar), 115.01 (CH, Ar), 114.55 (CN), 84.16 (C), 55.41 (OCH3), 44.15 (NCH2CH3), 12.30 (NCH2CH3), 11.15 (NCH2CH3).

Second diastereoisomer:

1H NMR δ (500 MHz, CDCl3) 7.37 (2H, d, J = 8.8 Hz, ArH), 6.99 (2H, d, J = 8.8 Hz, ArH), 3.84 (3H, s, OCH3), 3.73 (1H, dq, J = 13.6 and 7.1 Hz, NCH2CH3), 3.50 (1H, dq, J = 13.6 and 7.1 Hz, NCH2CH3), 3.24 (1H, m, NCH2CH3), 3.18 (1H, dq, J = 14.4 and 7.1 Hz, NCH2CH3), 1.31 (3H, t, J = 7.1 Hz, NCH2CH3), 0.88 (3H, t, J = 7.1 Hz, NCH2CH3).

13C NMR δ (125 MHz, CDCl3) 166.34 (Et3N-C=O), 161.45 (C-OMe), 127.52 (CH, Ar), 124.75 (C, Ar), 115.11 (CH, Ar), 114.63 (CN), 81.68 (C), 55.53 (OCH3), 45.47 (NCH2CH3), 44.75 (NCH2CH3), 12.35 (NCH2CH3), 11.23 (NCH2CH3).

6a-Chloro-3-diethylamino-3a,6-di(4-methoxyphenyl)-isothiazolino[4,5-d]isoxazolin-1,1-dioxide (22f)

Using the procedure above for compound (22b), 5-chloro-3-diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (14a) (27 mg; 0.08 mmol), 4-methoxybenzohydroximoyl chloride (15 mg; 0.08 mmol) and triethylamine (12 μL; 8.7 mg; 0.09 mmol) gave the crude product as a white oily solid (85 mg). Purification by gravity silica chromatography (PE/EtOAc: 3/1) afforded the product as a yellow oil (22 mg; 56%).

1H NMR δ (500 MHz, CDCl3) 7.99 (2H, d, J = 8.8 Hz, ArH), 7.57 (1H, bs, ArH), 7.00 (3H, bs, ArH), 6.93 (2H, d, J = 8.8 Hz, ArH), 3.85 (3H, s, OCH3), 3.85 (3H, s, OCH3), 3.77 (1H, dq, J = 13.6 and 7.0 Hz, NCH2CH3), 3.40 (1H, dq, J = 14.2 and 7.0 Hz, NCH2CH3), 3.36 (1H, dq, J = 13.6 and 7.0 Hz, NCH2CH3), 3.15 (1H, dq, J = 14.2 and 7.0 Hz, NCH2CH3), 1.26 (3H, t, J = 7.0 Hz, NCH2CH3), 1.03 (3H, t, J = 7.0 Hz, NCH2CH3).

13C NMR δ (125 MHz, CDCl3) 162.94 (C-NEt2), 161.74 (C-OMe), 160.94 (C-OMe), 154.81 (C-N), 130.42 (CH, Ar), 127.95 (CH, Ar), 127.22 (CH, Ar), 123.70 (C, Ar), 117.36 (C, Ar), 114.51 (CH, Ar), 113.77 (CH, Ar), 101.01 (C (ring junction)), 90.36 (C-CI (ring junction)), 55.36 (OCH3), 55.33 (OCH3), 44.80 (NCH2CH3), 44.10 (NCH2CH3), 12.81 (NCH2CH3), 11.17 (NCH2CH3).

3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (13a) (100 mg; 0.34 mmol) and benzohydroximoyl chloride (53 mg; 0.34 mmol) were suspended in dry diethyl ether (5 mL). Triethylamine (47 μL; 34 mg; 0.34 mmol) in dry diethyl ether (10 mL) was added drop-wise to the mixture over 5 to 6 hours. The mixture was stirred overnight (20 hours) under nitrogen, filtered, and the solvent evaporated under reduced pressure to give the crude product as a pale yellow solid (170 mg). It was purified by gravity silica chromatography (PE/EtOAc: 2/1) to give the product as a white fluffy solid (99 mg; 71%; m.p. = 78 – 80 °C).
Using the procedure above for compound (22b), 5-bromo-3-diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (15a) (102 mg; 0.27 mmol), 4-methoxybenzohydroximoyl chloride (51 mg; 0.27 mmol) and triethylamine (38 μL; 27 mg; 0.27 mmol) gave a crude product which was purified by gravity silica chromatography (PE/EtOAc: 3:1) to give the product as an orange oil (77 mg; 54%).

\[ \text{M + Na}^+ \]

\[ \text{M + Na}^+ \] (m/z) 528.1 [M + Na]^+*, 1033.3 [2M + Na]^+*, 1538.4 [3M + Na]^+*

HRMS (m/z): [M + Na]^+ for C_{23}H_{27}N_{3}NaO_{3}S measured 528.1233 measured 528.1248.

The structure of this compound (22b-D2) was confirmed by X-ray crystallographic analysis.31

Diastereoisomer 2:

\[ \text{M + Na}^+ \]

\[ \text{M + Na}^+ \] (m/z) 528.1 [M + Na]^+*, 1033.3 [2M + Na]^+*, 1538.4 [3M + Na]^+*

HRMS (m/z): [M + Na]^+ for C_{23}H_{27}N_{3}NaO_{3}S measured 528.1233 measured 528.1243.

The structure of this compound (22b-D1) was confirmed by X-ray crystallographic analysis.31

3-Dietylamino-6a-methanesulfonyl-3a,6-dii(4-methoxyphenyl)-isothiazolino[4,5-d]isoxazol-1,1-dioxide (22h)

Using the procedure above for compound (22b), 3-diethylamino-5-methanesulfonyl-1-(4-methoxyphenyl)-isothiazol-1,1-dioxide (17a) (100 mg; 0.28 mmol), 4-methoxybenzohydroximoyl chloride (52 mg; 0.28 mmol) and triethylamine (39 μL; 28 mg; 0.28 mmol) gave the crude product as a yellow oil (141 mg). Purification by gravity silica chromatography (hexane/EtOAc: 2:1) afforded the two diastereoisomers, one as a yellow solid (48 mg; 34%; m.p. = 192 – 193 °C) and the other as a yellow solid (26 mg, 18%; m.p. = 207 – 209 °C) in a 2:1 ratio.

Diastereoisomer 1:

\[ \text{M + Na}^+ \]

\[ \text{M + Na}^+ \] (m/z) 528.1 [M + Na]^+*, 1033.3 [2M + Na]^+*, 1538.4 [3M + Na]^+*

HRMS (m/z): [M + Na]^+ for C_{23}H_{27}N_{3}NaO_{3}S measured 528.1233 measured 528.1243.

The structure of this compound (22b-D1) was confirmed by X-ray crystallographic analysis.31

3-Dietylamino-6a-methanesulfonyl-3a,6-di(4-methoxyphenyl)-isothiazolino[4,5-d]isoxazol-1,1-dioxide (22i)

Using the procedure above for compound (22b), 3-diethylamino-5-methanesulfonyl-1-(4-methoxyphenyl)-isothiazol-1,1-dioxide (6a) (101 mg; 0.27 mmol), 4-methoxybenzohydroximoyl chloride (50 mg; 0.27 mmol) and triethylamine (38 μL; 28 mg; 0.27 mmol) gave the crude product as a yellow solid (159 mg). Purification by gravity silica chromatography (PE/EtOAc: 2:1) afforded the product as a white solid (96 mg; 68%; m.p. = 198 – 199 °C).

\[ \text{M + Na}^+ \]

\[ \text{M + Na}^+ \] (m/z) 528.1 [M + Na]^+*, 1033.3 [2M + Na]^+*, 1538.4 [3M + Na]^+*

HRMS (m/z): [M + Na]^+ for C_{23}H_{27}N_{3}NaO_{3}S measured 528.1233 measured 528.1243.

The structure of this compound (22b-D1) was confirmed by X-ray crystallographic analysis.31
Frequency, NCH$_2$CH$_3$, 3.31 (1H, dq, J = 13.6 and 7.0 Hz, NCH$_2$CH$_3$), 2.99 (1H, dq, J = 14.2 and 7.0 Hz, NCH$_2$CH$_3$), 1.28 (3H, t, J = 7.0 Hz, NCH$_2$CH$_3$).

$^1$C NMR δ (100 MHz, CDCl$_3$) 163.73 (C=N), 161.76 (C-OMe), 161.74 (C-OMe), 152.71 (Ar-C=N-O), 133.00 (CH, Ar), 129.99 (CH, Ar), 128.57 (CH, Ar), 120.03 (C, Ar), 118.67 (C, Ar), 114.88 (CH, Ar), 99.87 (C (ring junction)), 98.44 (C-SO$_2$Me), 55.50 (OCH$_3$), 55.28 (OCH$_3$), 45.21 (NCH$_2$CH$_3$), 43.94 (NCH$_2$CH$_3$), 42.76 (SO$_2$CH$_3$), 12.92 (NCH$_2$CH$_3$), 11.02 (NCH$_2$CH$_3$).

IR $\nu$ max (cm$^{-1}$): 2935, 1603, 1513, 1332, 1308, 1259, 1183, 1169, 1141, 1026, 966, 835.


HRMS (m/z): [M + Na]$^+$ for C$_{31}$H$_{32}$N$_2$O$_4$S$_2$ calculated 544.1183 measured 544.1197.

The structure of this compound was confirmed by X-ray crystallographic analysis.

3-Diethylamino-6-α-methanesulfinyl-3α-(4-methoxyphenyl)isothiazolino[4,5-d]triazolin-1,1-dioxide (23a/b)

3-Diethylamino-5-methanesulfinyl-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (17a) (200 mg, 0.56 mmol) was dissolved in dry acetonitrile (10 mL), and sodium azide (38 mg, 0.58 mmol) was added to the mixture. The whole was stirred at RT under nitrogen, and the reaction was monitored by TLC. After 30 hours, the solvent was removed in vacuo to give the crude product as a yellow solid (257 mg). Purification by flash silica chromatography (PE/EtOAc: gradient elution 1/1, 1/2, 1/4) gave the product as two separable diastereoisomers (23a) (50 mg, 22%, m.p. = 133 °C) and (23b) (60 mg, 27%, m.p. = 142 – 143 °C).

Diastereoisomer (23a):

$^1$H NMR δ (500 MHz, CDCl$_3$) 12.16 (1H, bs, NH), 7.44 – 7.46 (1H, m, ArH), 7.39 – 7.41 (1H, m, ArH), 6.97 (2H, d, J = 8.7 Hz, ArH), 3.85 (3H, s, OCH$_3$), 3.74 (1H, dq, J = 14.5 and 7.0 Hz, NCH$_2$CH$_3$), 3.49 (1H, dq, J = 13.5 and 7.0 Hz, NCH$_2$CH$_3$), 3.39 (1H, dq, J = 13.5 and 7.0 Hz, NCH$_2$CH$_3$), 3.37 (1H, dq, J = 14.5 and 7.0 Hz, NCH$_2$CH$_3$), 2.11 (3H, s, CH$_3$SO), 1.17 (3H, t, J = 7.0 Hz, NCH$_2$CH$_3$), 0.65 (3H, t, J = 7.0 Hz, NCH$_2$CH$_3$).

$^1$C NMR δ (125 MHz, CDCl$_3$) 161.66 (C=N), 160.90 (C-OMe), 128.85 (CH, Ar), 128.16 (CH, Ar), 126.97 (C, Ar), 115.03 (CH, Ar), 98.90 (C), 96.43 (C-SO$_2$Me), 55.43 (OCH$_3$), 45.56 (NCH$_2$CH$_3$), 43.83 (NCH$_2$CH$_3$), 33.27 (CH$_3$SO), 12.51 (NCH$_2$CH$_3$), 11.28 (NCH$_2$CH$_3$).

$^1$H NMR δ (400 MHz, DMSO-D$_6$) 13.78 (1H, bs, NH), 7.43 – 7.45 (1H, m, ArH), 7.19 – 7.07 (3H, m, ArH), 3.78 (3H, s, OCH$_3$), 3.67 (1H, dq, J = 14.3 and 7.0 Hz, NCH$_2$CH$_3$), 3.43 – 3.32 (3H, m, NCH$_2$CH$_3$), 1.99 (3H, s, CH$_3$SO), 1.07 (3H, t, J = 7.0 Hz, NCH$_2$CH$_3$), 0.56 (3H, t, J = 7.0 Hz, NCH$_2$CH$_3$).

HRMS (m/z): [M + Na]$^+$ for C$_{31}$H$_{32}$N$_2$O$_4$S$_2$ calculated 544.1183 measured 544.1197.

The structure of this compound was confirmed by X-ray crystallographic analysis.

3-Diethylamino-6a-methanesulfinyl-3a-(4-methoxyphenyl)isothiazolino[4,5-d]pyrazolin-1,1-dioxide (24)

3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (13a) (100 mg, 0.34 mmol) and α-chlorobenzaldehyde phenyldrazonate (117 mg, 0.51 mmol) were suspended in dry ether (5 mL). Triethylamine (71 mL, 51 mg, 0.51 mmol) in dry ether (15 mL) was added drop-wise to the mixture over 4 to 5 hours. The whole was stirred under nitrogen at RT for 72 hours and then at reflux for 22 hours. The mixture was filtered, and the solvent evaporated to give the crude product as a pale brown oil which was purified by gravity silica chromatography
(PE/EntOAc: gradient elution 3/1, 2/1) to give the product as a yellow solid (68 mg, 41%, m.p. = 210 – 211 °C).

1H NMR δ (500 MHz, CDCl₃) 7.75 – 7.85 (2H, m, CH, Ph), 7.50 – 7.52 (2H, m, CH, Ph), 7.30 – 7.40 (8H, m, CH, Ph), 7.00 (2H, d, J = 9.00 Hz, CH, Ar), 4.90 (1H, s, CH (ring junction)), 3.82 (3H, s, OCH₃), 3.56 (1H, dq, J = 13.6 and 7.0 Hz, NCH₂CH₃), 3.01 (1H, dq, J = 13.6 and 7.0 Hz, NCH₂CH₃), 2.96 (1H, dq, J = 14.2 and 7.0 Hz, NCH₂CH₃), 1.99 (1H, dq, J = 14.2 and 7.0 Hz, NCH₂CH₃), 0.78 (3H, t, J = 7.0 Hz, NCH₂CH₃), 0.33 (3H, t, J = 7.0 Hz, NCH₂CH₃).

13C NMR δ (125 MHz, CDCl₃) 162.11 (C=N), 159.87 (C-OMe), 144.26 (C), 143.01 (C), 132.02 (C), 130.23 (C), 129.76 (CH, Ar), 129.61 (CH, Ar), 129.13 (CH, Ar), 128.92 (CH, Ar), 128.74 (CH, Ar), 126.49 (CH, Ar), 125.98 (C), 115.05 (CH, Ar), 85.19 (C (ring junction)), 82.84 (CH (ring junction)), 55.43 (OCH₃), 46.28 (NCH₂CH₃), 44.16 (NCH₂CH₃), 11.24 (NCH₂CH₃), 10.51 (NCH₂CH₃).

IR ν_max (cm⁻¹) 2979, 1574, 1508, 1492, 1444, 1357, 1308, 1250, 1171, 1133, 1096, 1031, 977, 911, 894, 836, 781, 755, 729, 705, 692.

MS (m/z): 511.2 [M + Na][⁺], 999.4 [2M + Na][⁺].

HRMS (m/z): [M + Na][⁺] for C₂₂H₂₈N₄NaO₅S calculated 511.1774 measured 511.1778.

The structure of this compound was confirmed by X-ray crystallographic analysis. 31

Conclusions

Our initial aim was to use Clerici’s thiazete 1,1-dioxide (5a) as a novel substrate for 1,3-dipolar and cyclopropenone based cycloadditions. We have shown, disappointingly, that the thiazete 1,1-dioxide (5a) is not reactive towards 1,3-dipoles or cyclopropenones, in marked contrast to the 1-azetine system, but that it does undergo rearrangement into the previously unreported 1,2,3-oxathiazolin-2-oxide (21). However, we have produced sixteen new isothiazoloisoxazoles and four new isothiazole 1,1-dioxides building upon the route used to access the thiazete 1,1-dioxide (5a). We have established that the previously unreported sulfoxide substituted isothiazole 1,1-dioxide (17a) produced a new isothiazolotriazole upon reaction with sodium azide, and we suggest that this offers some mechanistic insight into the conversion of the corresponding sulfone substituted isothiazole 1,1-dioxide (6a) into the thiazete 1,1-dioxide (5a). We have also produced one new isothiazolopyrazole, establishing the reactivity of isothiazole 1,1-dioxides towards nitrilimines, an aspect that we aim to explore further. The structure of this isothiazolopyrazole together with that of the isothiazolotriazole and four of the isothiazoloisoxazoles were confirmed, for the first time, by X-ray crystallographic studies. Four of our new isothiazoloisoxazoles and the isothiazolotriazole showed restricted rotation of the sterically hindered bridgehead substituents. A further subset of four of our new isothiazoloisoxazoles showed promising low μM activity against a human breast carcinoma cell line and we are currently exploring this aspect of our findings further.

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Notes

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Electronic Supplementary Information (ESI) available: Synthesis and spectroscopic data for compounds 5a, 6a, 8a, 9a, 9e – f, 10a, 10c – f, 11a, 11c – f, 13a, 13c – f, 15a, 16a, 22a, 22c – e and 22k – t. Copies of the 1H and 13C NMR spectra for previously unreported compounds 21, 22b, 22c, 22f – t, 23 and 24. Summary of X-ray crystallographic data for compounds 22a, 22h (diastereoisomer 1), 22h (diastereoisomer 2), 22i, 23b and 24.

References

31 Crystallographic data has been deposited at the Cambridge Crystallographic Data Centre. Copies of these data can be obtained free of charge on application to CCDC, 12, Union Road, Cambridge, CB2 1EZ, UK at www.ccdc.cam.ac.uk/data_request/cif; CCDC deposit numbers: Compound (22a): 1441502; compound (22h), diastereoisomer 1: 1426769; compound (22h), diastereoisomer 2: 1426768; compound (22i): 1426767; compound (23b): 1420006; compound (24): 1441503. See supplementary files for a summary of the crystallographic data.