Synthesis of a Library of 1,5,2-Dithiazepine 1,1-Dioxides. Part 1: A One-Pot Sulfonylation/Thia-Michael Protocol

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Abstract

A novel one-pot sulfonylation/intramolecular thia-Michael protocol is reported for the synthesis of 1,5,2-dithiazepine 1,1-dioxides. Sulfonylation between cysteine ethyl ester/cysteamine and 2-chloroethanesulfonyl chloride, followed by \textit{in situ} intramolecular thia-Michael addition, was achieved and afforded the titled 1,5,2-dithiazepine-1,1-dioxide scaffolds. Diversification was demonstrated for future library synthesis.

Heterocycles have a storied history in drug development due to their diverse pharmacological properties, which when coupled with advances in high-throughput screening and the need for new pharmaceutical leads, drive discovery efforts for their efficient synthesis.\textsuperscript{1} Hetero Michael reactions aspire to this goal, and have been broadly used in the synthesis of azacycles,\textsuperscript{2} oxacycles,\textsuperscript{3, 4} thiacycles,\textsuperscript{5} and \textit{bis}-heterocycles,\textsuperscript{6} all of which can be characterized as versatile pathways that are mild, catalytic, and adhere to atom and step economy. Vinyl sulfones are one particular class of Michael acceptors that have been well documented in the literature,\textsuperscript{7} however, their vinyl sulfonamide counterparts have assumed a far less prominent role. To this end, we have utilized the hetero-Michael addition on vinyl sulfonamides to synthesize a series of sultams (cyclic sulfonamides, Scheme 1).\textsuperscript{8} These efforts include a “click, click, cyclize” strategy in the synthesis of 1,4,5-oxathiazepane 4,4-dioxides utilizing an intramolecular oxa-Michael pathway,\textsuperscript{8a,b} an automated synthesis of 1,2,5-thiadiazepane 1,1-dioxide via an aza-Michael pathway,\textsuperscript{8c} a double aza-Michael protocol in the synthesis of 1,2,5-thiadiazepane 1,1-dioxide,\textsuperscript{8d,e} and a Heck-aza-Michael strategy in the synthesis of isoindoline/tetrahydroisoquinoline-based tricyclic sultams.\textsuperscript{8f,g} Taken collectively, use of “click” sulfonylation,\textsuperscript{9} “click” sulfonamide alkylation and subsequent Michael additions greatly simplify sultam construction. In this context, we herein report a one-pot sulfonylation/intramolecular thia-Michael protocol, which combines the “click” sulfonylation and the cyclization steps in one pot, to readily assemble the titled sultam scaffolds.

As a precursor of the \textit{bis}-electrophilic synthon vinylsulfonyl chloride, 2-chloroethanesulfonyl chloride (I) can react with a wide range of \textit{bis}-nucleophilic synthons, such as substituted 2-amino alcohols, to generate 7-membered sultams.\textsuperscript{8} Previous oxa-Michael studies from our laboratories has shown that the use of a tertiary sulfonamide is

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necessary for the Michael addition to take place. However, when 1 was treated with cysteine ethyl ester (2a) or cysteamine (2b), intramolecular thia-Michael and sulfonylation occur simultaneously, leading to a one-pot synthesis of 1,5,2-dithiazepine 1,1-dioxide scaffolds 3 that bear free sulfonamide N-H groups (Scheme 1). A survey of base, additive, solvent and temperature (Entries 1 to 8, Table 1) showed 3.5 equivalent of Et$_3$N, 0.1 equivalent of DMAP, 40 °C in CH$_2$Cl$_2$ gives the highest yield. Although the yield in this protocol is only moderate, the reaction is carried out under mild conditions and the products were conveniently recrystallized and isolated as colorless needles. We assume the moderate yield may be caused by the polymerization via intermolecular pathways, as some residue that didn't dissolve in any solvent was observed during recrystallization, as well as the fact that slightly enhanced yield in more diluted concentration (Entry 9). Another possible reason accounting for the difficulty in approving the yield could be the decomposition of cysteine ethyl ester. It was supported by the detection of hydrogen sulfide smell, which is void in either starting cysteine ethyl ester or the cyclized product. To check this possibility, the ratio of sulfonyl chloride and cysteine ethyl ester was changed. In the case of excess sulfonyl chloride (Entry 10), the yield was similar to the original result (Entry 3), while when cysteine ethyl ester was in excess the yield was increased to 42% (Entry 11). Further increasing cysteine ethyl ester to 4 equivalents resulted in an inseparable byproduct along with the product (not shown). Finally, the reaction was carried out up to 40-gram scale (cysteine ethyl ester) using the condition in Entry 3, and roughly 20 grams of the desired product was obtained after recrystallization (CHCl$_3$) in a single reaction step (Entry 12). The structure of 3b was confirmed via X-ray crystallography (Figure 1).

Notably, the only report of synthesis of 1,5,2-dithiazepane 1,1-dioxide (3a) involves the usage of 2,2′-dithiobis(ethylamine) dihydrochloride in a two-step sequence using two chromatographic separations (Scheme 2). With the convenient synthesis of sultam 3 in hand, various diversification pathways were explored as outlined in Scheme 3. Benzylation of sultam scaffolds 3 using substituted benzyl bromides gave products 4 in good yield. In addition, benzylation of 3a required Cs$_2$CO$_3$ in DMF, but milder conditions (K$_2$CO$_3$ in MeCN) were sufficient for substrate 3b presumably due to the electron withdrawing ester group in 3b. Treating of 3 with acyl chloride, in the presence of Et$_3$N and DMAP resulted in acyl-products 5. Alternatively, reduction of the ester group of 3b followed by isocyanate coupling with the resulting alcohol provided carbamate 6. Finally, amides 7 were synthesized via a two-step sequence of benzylation and direct amidation of the ester.

In summary, a one-pot sulfonylation/intramolecular thia-Michael protocol was developed for the synthesis of 1,5,2-dithiazepine 1,1-dioxide scaffold on multi-gram scale, incorporating stereosemistry and additional handles for further diversification. A demonstrative library was generated from the scaffolds. The compounds produced are currently being broadly screened within the NIH Molecular Library Screening Network (NIH-MLSCN) and additional biological collaborators.

**Experimental**

All reactions were carried out under argon atmosphere. Stirring was achieved with oven-dried magnetic stir bars. Et$_2$O, toluene, THF and CH$_2$Cl$_2$ were either purchased through Sigma-Aldrich or purified by passage through the Solv-Tek purification system employing activated Al$_2$O$_3$ (Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* 1996, 15, 1518–1520). Et$_3$N was purified by passage over basic alumina or distilled over CaH and stored over KOH. Flash column chromatography was performed with Sorbent Technologies (30930M-25, Silica Gel 60A, 40-63 um). Thin layer chromatography was performed on
silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. $^1$H, $^{13}$C NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz, 100 MHz respectively as well as a Bruker DRX-500 spectrometer operating at 500 MHz, 125 MHz respectively and an Avance AV-III 500 with a dual carbon/proton (CPDUL) cryoprobe operating at 500 MHz, 125 MHz respectively. Observed rotations at 589 nm were measured using AUTOPOL IV Model automatic polarimeter. Weights were taken on a Flexiweigh Automatic Weigher; weight tolerance +/- 0.3 mg. Samples were concentrated on a GeneVac EZ personal evaporator and placed under high vacuum for ≥ 2 hours before final weights were taken.

**General procedure for the one-pot sulfonylation/intramolecular thia-Michael protocol**

2-Chloroethanesulfonyl chloride (20.9 mL, 0.2 mol) was added drop wise to a stirred solution of cysteine ethyl ester (40.9 g, 1.1 equiv.) or cysteamine hydrochloride (25.0 g, 1.1 equiv.), Et$_3$N (111.3 mL, 4 equiv.) and DMAP (2.44 g, 0.1 equiv.) in CH$_2$Cl$_2$ (500 mL) at 0ºC. After addition, the reaction was allowed to warm to room temperature and stirred overnight. The mixture was washed with 1 M HCl, brine, dried (Na$_2$CO$_3$), and concentrated under reduced pressure. The crude mixture was recrystallized with CHCl$_3$ to afford the product $3a$ or $3b$ as colorless needles.

**1,5,2-dithiazepane 1,1-dioxide (3a).**

Colorless needles, yield 32%. $^1$H NMR (500 MHz, CDCl$_3$) δ 4.95–4.77 (brs, 1H), 3.55–3.47 (m, 2H), 3.29 (t, $J$ = 6.3 Hz, 2H), 3.10 (t, $J$ = 6.4 Hz, 2H), 2.95–2.86 (m, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 58.9, 41.8, 35.1, 28.1.

**($R$)-ethyl 1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (3b)**

Colorless needles, yield 41%. mp 168–169 ºC. [α]$_D^{20}$-64.8 (c 0.75, CH$_2$Cl$_2$). FTIR: 2947, 1491, 1339, 1140, 1109, 758 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.63 (s, 1H), 4.33–4.24 (m, 3H), 3.72 (ddd, $J$ = 14.4, 3.7 Hz, 1H), 3.53 (dd, $J$ = 15.8, 5.8 Hz, 1H), 3.44 (dd, $J$ = 15.8, 2.9 Hz, 1H), 3.41–3.34 (m, 1H), 2.92–2.88 (m, 2H), 1.31 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 169.6, 62.9, 59.3, 54.1, 37.3, 28.1, 14.1. HRMS (ESI) m/z calculated for C$_7$H$_{13}$NNaO$_4$S$_2$ 262.0184 (M+Na)$^+$, found 262.0184.

**General procedure for the synthesis of 4a-c from scaffolds 3a**

To a stirred solution of 3a (0.2 mmol, 1 equiv.) and benzyl bromide (0.22 mmol, 1.1 equiv.) in DMF (1 mL) was added Cs$_2$CO$_3$ (0.3 mmol, 1.5 equiv.). The mixture was stirred at 60 ºC overnight, before quenching with addition of H$_2$O. The mixture was diluted with Et$_2$O, washed with H$_2$O and brine, dried (Na$_2$CO$_3$), and concentrated under reduced pressure. The crude product was purified via flash chromatography.

**2-(4-bromobenzyl)-1,5,2-dithiazepane 1,1-dioxide (4a)**

White solid, yield 68%. mp 164–165 ºC. FTIR: 2924, 2887, 1331, 1142, 914 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.52–7.46 (m, 2H), 7.28 (d, $J$ = 8.4 Hz, 2H), 4.48 (s, 2H), 3.52–3.45 (m, 2H), 3.19 (dd, $J$ = 9.8, 3.5 Hz, 2H), 3.10 (dd, $J$ = 9.7, 3.6 Hz, 2H), 2.94–2.88 (m, 2H), 1.31 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 135.1, 131.8, 129.9, 121.9, 55.9, 54.1, 45.5, 34.4, 27.5. HRMS (ESI) m/z calculated for C$_{11}$H$_{15}$BrNO$_2$S$_2$ 335.9728 (M+H)$^+$, found 335.9733.

**2-(3-chlorobenzyl)-1,5,2-dithiazepane 1,1-dioxide (4b)**

White solid, yield 89%. mp 125–126 ºC. FTIR: 2924, 1327, 1140, 1121, 854, 735, 494 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.42–7.39 (m, 1H), 7.30 (t, $J$ = 1.4 Hz, 3H), 4.52 (s, 2H), 3.54–3.47 (m, 2H), 3.22 (t, $J$ = 6.3 Hz, 2H), 3.12 (dd, $J$ = 9.6, 3.5 Hz, 2H), 2.95–2.89
(m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 138.2, 134.7, 130.0, 128.2, 128.2, 126.3, 56.0, 54.2, 45.6, 34.5, 27.5. HRMS (ESI) $m/z$ calculated for C$_{11}$H$_5$NO$_2$S$_2$Cl 292.0233 (M+H)$^+$, found 292.0222.

2-(3-methylbenzyl)-1,5,2-dithiazepane 1,1-dioxide (4c)

White solid, yield 85%. mp 88–90 °C. FTIR: 2919, 1335, 1146, 1124, 854, 729 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.26–7.21 (m, 2H), 7.19 (d, $J$ = 7.6 Hz, 1H), 7.13 (d, $J$ = 7.5 Hz, 1H), 4.51 (s, 2H), 3.54–3.47 (m, 2H), 3.22 (t, $J$ = 6.4 Hz, 2H), 3.11 (dd, $J$ = 9.7, 3.4 Hz, 2H), 2.94–2.89 (m, 2H), 2.37 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 138.5, 135.9, 128.9, 128.7, 128.5, 125.3, 56.0, 54.5, 45.2, 34.5, 27.5, 21.4. HRMS (ESI) $m/z$ calculated for C$_{12}$H$_7$NO$_2$S$_2$Na 294.0598 (M+H)$^+$, found 294.0596.

General procedure for the synthesis of 4d–f from scaffolds 3b

To a stirred solution of 3b (0.20 mmol, 1 equiv.) and benzyl bromide (0.22 mmol, 1.1 equiv.) in CH$_3$CN (1 mL) was added K$_2$CO$_3$ (0.30 mmol, 1.5 equiv.). The mixture was stirred at 60 °C overnight, before quenching with addition of H$_2$O. The mixture was diluted with Et$_2$O, washed with H$_2$O and brine, dried (Na$_2$CO$_3$), and concentrated under reduced pressure. The crude product was purified via flash chromatography.

(4R)-ethyl 2-benzyl-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (4d)

White solid, yield 71%. $[\alpha]_D^{20}$ -31.7 (c 0.70, CH$_2$Cl$_2$). FTIR: 2982, 2926, 1732, 1339, 1148, 854, 727, 698 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.53–7.46 (m, 2H), 7.40–7.30 (m, 3H), 4.78 (d, $J$ = 14.6 Hz, 1H), 4.49 (d, $J$ = 14.6 Hz, 1H), 4.09–4.02 (m, 2H), 3.72 (dd, $J$ = 11.0, 7.0 Hz, 1H), 3.59 (dd, $J$ = 15.6, 11.0 Hz, 1H), 3.43 (dd, $J$ = 15.6, 7.0 Hz, 1H), 3.29 (dd, $J$ = 14.5, 12.4, 4.2 Hz, 1H), 2.98 (dd, $J$ = 15.2, 12.4, 2.8 Hz, 1H), 2.90 (dd, $J$ = 15.3, 3.6, 3.6 Hz, 1H), 1.17 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 169.7, 135.1, 129.6, 128.5, 128.2, 61.6, 59.6, 56.2, 55.3, 37.5, 28.4, 13.9. HRMS (ESI) $m/z$ calculated for C$_{14}$H$_{15}$NO$_2$S$_2$K 368.0393 (M+K)$^+$, found 303.0392.

(4R)-ethyl 2-(4-methylbenzyl)-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (4e)

Yellow solid, yield 74%. mp 85–86 °C. $[\alpha]_D^{20}$ -19.5 (c 1.00, CH$_2$Cl$_2$). FTIR: 2980, 2924, 1728, 1340, 1146, 854 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 (d, $J$ = 8.0 Hz, 2H), 7.16 (d, $J$ = 7.8 Hz, 2H), 4.73 (d, $J$ = 14.4 Hz, 1H), 4.47 (d, $J$ = 14.4 Hz, 1H), 4.06 (q, $J$ = 7.1 Hz, 2H), 3.71 (dd, $J$ = 10.9, 7.1 Hz, 1H), 3.58 (dt, $J$ = 14.5, 3.1 Hz, 1H), 3.52 (dd, $J$ = 15.6, 11.0 Hz, 1H), 3.41 (dd, $J$ = 15.6, 7.1 Hz, 1H), 3.28 (dd, $J$ = 14.5, 12.2, 4.3 Hz, 1H), 2.97 (dd, $J$ = 15.0, 12.2, 2.8 Hz, 1H), 2.88 (dt, $J$ = 15.3, 3.9 Hz, 1H), 2.35 (s, 3H), 1.18 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 169.8, 138.0, 131.9, 129.5, 129.1, 61.6, 59.3, 55.8, 55.3, 37.5, 28.3, 21.1, 13.9. HRMS (ESI) $m/z$ calculated for C$_{15}$H$_{15}$NO$_2$S$_2$Na 366.0810 (M +Na)$^+$, found 366.0813.

(4R)-ethyl 2-(2-fluorobenzyl)-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (4f)

Yellow oil, yield 81%. $[\alpha]_D^{20}$ -6.4 (c 1.00, CH$_2$Cl$_2$). FTIR: 2982, 2926, 1732, 1493, 1342, 1229, 1148, 854, 760 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.60 (td, $J$ = 7.6, 1.7 Hz, 1H), 7.35–7.29 (m, 1H), 7.16 (td, $J$ = 7.5, 1.1 Hz, 1H), 7.11–7.04 (m, 1H), 4.85 (d, $J$ = 15.1 Hz, 1H), 4.55 (d, $J$ = 15.2 Hz, 1H), 4.10 (qd, $J$ = 7.1, 2.3 Hz, 2H), 3.81 (dd, $J$ = 10.6, 7.4 Hz, 1H), 3.54 (dd, $J$ = 14.4, 3.0, 3.0 Hz, 1H), 3.50–3.36 (m, 2H), 3.20 (dd, $J$ = 14.4, 12.5, 4.1 Hz, 1H), 2.96–2.88 (m, 1H), 2.82 (dd, $J$ = 15.3, 3.7, 3.7 Hz, 1H), 1.18 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 169.8, 161.2 (d, $J_{CF}$ = 246.7 Hz), 132.3 (d, $J_{CF}$ = 3.8 Hz), 130.1 (d, $J_{CF}$ = 8.3 Hz), 124.2 (d, $J_{CF}$ = 3.6 Hz), 122.5 (d, $J_{CF}$ = 14.6 Hz), 115.4 (d, $J_{CF}$ = 21.9 Hz), 61.6, 60.1 (d, $J_{CF}$ = 1.2 Hz), 55.6, 49.1 (d, $J_{CF}$ = 2.9 Hz), 37.1, 28.2,
13.9. HRMS (ESI) m/z calculated for C_{14}H_{16}FNO_{4}S_{2}Na 370.0559 (M+Na)^{+}, found 370.0555.

**General procedure for the synthesis of 5 from scaffolds 3**

To a stirred solution of 3 (0.20 mmol, 1 equiv.), Et_{3}N (0.60 mmol, 3 equiv.), DMAP (0.02 mmol, 0.1 equiv.) in CH_{2}Cl_{2} (1 mL) was slowly added acyl chloride (0.22 mmol, 1.1 equiv.) at 0 °C. The mixture was kept stirring at 0 °C for 1 h, before quenching with addition of H_{2}O. The mixture was diluted with Et_{2}O, washed with H_{2}O and brine, dried (Na_{2}CO_{3}), and concentrated under reduced pressure. The crude product was purified via flash chromatography.

1-(1,1-dioxido-1,5,2-dithiazepan-2-yl)ethanone (5a)

Yellow solid, yield 88%. mp 104–105 °C. FTIR: 2984, 2926, 1697, 1352, 1157, 849 cm\(^{-1}\). \(^{1}\)H NMR (400 MHz, CDCl\(_{3}\)) \(\delta\) 3.99 (d, \(J = 6.7\) Hz, 2H), 3.68–3.62 (m, 2H), 3.10 (d, \(J = 6.6\) Hz, 2H), 2.92–2.87 (m, 2H), 2.46 (s, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_{3}\)) \(\delta\) 171.0, 55.4, 42.9, 33.5, 27.4, 25.1. HRMS (ESI) m/z calculated for C\(_{9}\)H\(_{11}\)NO\(_{3}\)S\(_{2}\)Na 232.0078 (M+Na)^{+}, found 232.0078.

1-(1,1-dioxido-1,5,2-dithiazepan-2-yl)-2,2-dimethylpropan-1-one (5b)

White solid, yield 87%. mp 125–126 °C. FTIR: 2976, 2935, 1688, 1352, 1157, 1095 cm\(^{-1}\). \(^{1}\)H NMR (400 MHz, CDCl\(_{3}\)) \(\delta\) 3.93 (t, \(J = 6.5\) Hz, 2H), 3.90–3.83 (m, 2H), 2.36 (t, \(J = 6.5\) Hz, 2H), 2.91–2.86 (m, 2H), 1.35 (s, 9H). \(^{13}\)C NMR (126 MHz, CDCl\(_{3}\)) \(\delta\) 181.2, 54.2, 44.5, 41.7, 35.9, 28.8, 28.0. HRMS (ESI) m/z calculated for C\(_{9}\)H\(_{11}\)NO\(_{3}\)S\(_{2}\)Na 274.0548 (M+Na)^{+}, found 274.0530.

(\(E\))-1-(1,1-dioxido-1,5,2-dithiazepan-2-yl)-3-phenylprop-2-en-1-one (5c)

White solid, yield 85%. mp 150–151 °C. FTIR: 2926, 1676, 1616, 1356, 1155, 1122 cm\(^{-1}\). \(^{1}\)H NMR (400 MHz, CDCl\(_{3}\)) \(\delta\) 7.84 (d, \(J = 15.4\) Hz, 1H), 7.60 (dd, \(J = 6.8, 2.8\) Hz, 2H), 7.48–7.41 (m, 2H), 4.15 (t, \(J = 6.6\) Hz, 2H), 3.71–3.65 (m, 2H), 3.15 (t, \(J = 6.6\) Hz, 2H), 2.93–2.87 (m, 2H). \(^{13}\)C NMR (126 MHz, CDCl\(_{3}\)) \(\delta\) 166.7, 147.3, 134.3, 130.8, 129.0, 128.5, 117.3, 56.8, 42.6, 33.9, 27.7. HRMS (ESI) m/z calculated for C\(_{13}\)H\(_{15}\)NO\(_{3}\)S\(_{2}\)Na 320.0391 (M+Na)^{+}, found 320.0393.

(R)-ethyl 2-pivaloyl-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (5d)

White solid, yield 81%. mp 152–153 °C. [\(\alpha\)]\(_{D}^{20}\) -102.2 (c 0.92, CH\(_{2}\)Cl\(_{2}\)). FTIR: 2954, 1738, 1690, 1358, 1159, 1111 cm\(^{-1}\). \(^{1}\)H NMR (500 MHz, CDCl\(_{3}\)) \(\delta\) 4.85 (dd, \(J = 9.2, 8.1\) Hz, 1H), 4.29 (qd, \(J = 7.1, 1.6\) Hz, 2H), 4.21 (ddd, \(J = 14.8, 9.2, 7.9\) Hz, 1H), 3.60 (dd, \(J = 15.7, 9.4\) Hz, 1H), 3.55–3.47 (m, 2H), 2.91 (dd, \(J = 2.9, 1.5\) Hz, 1H), 2.90 (d, \(J = 3.0\) Hz, 1H), 1.37 (s, 9H), 1.32 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_{3}\)) \(\delta\) 179.8, 168.9, 62.3, 57.4, 53.3, 41.6, 38.4, 28.8, 28.2, 14.0. HRMS (ESI) m/z calculated for C\(_{13}\)H\(_{15}\)NO\(_{3}\)S\(_{2}\)Na 346.0759 (M+Na)^{+}, found 346.0741.

(R)-ethyl 2-(3-methoxybenzoyl)-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (5e)

White solid, yield 76%. mp 112–113 °C. [\(\alpha\)]\(_{D}^{20}\) -83.2 (c 1.00, CH\(_{2}\)Cl\(_{2}\)). FTIR: 2981, 1740, 1690, 1364, 1231, 1161, 841, 746 cm\(^{-1}\). \(^{1}\)H NMR (500 MHz, CDCl\(_{3}\)) \(\delta\) 7.37 (t, \(J = 7.9\) Hz, 1H), 7.29 (dd, \(J = 7.6, 1.0\) Hz, 1H), 7.27–7.25 (m, 1H), 7.07 (ddd, \(J = 8.3, 2.6, 0.9\) Hz, 1H), 4.60 (dd, \(J = 10.0, 7.7\) Hz, 1H), 4.41–4.30 (m, 3H), 3.83 (s, 3H), 3.64 (dt, \(J = 14.9, 3.0\) Hz, 1H), 3.50 (dd, \(J = 15.6, 10.0\) Hz, 1H), 3.36 (dd, \(J = 15.6, 7.7\) Hz, 1H), 3.04–2.91 (m, 2H), 1.37 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_{3}\)) \(\delta\) 173.0, 168.6, 159.8, 135.1, 130.2,
(R)-ethyl 2-cinnamoyl-1,5,2-dithiazepane-3-carboxylate 1,1-dioxide (5f)

Yellow solid, yield 79%. mp 123–124 °C. [α]D20 -83.2 (c 1.00, CH2Cl2). FTIR: 2981, 1740, 1690, 1634, 1231, 1161, 841, 746 cm⁻¹. 1H NMR (400 MHz, CDCl3) δ 7.90 (d, J = 15.4 Hz, 1H), 7.64–7.58 (m, 2H), 7.53 (d, J = 15.4 Hz, 1H), 7.43 (dd, J = 5.1, 1.9 Hz, 3H), 5.56 (dd, J = 11.4, 6.4 Hz, 1H), 4.32 (dq, J = 10.7, 7.1 Hz, 1H), 4.23 (dq, J = 10.7, 7.1 Hz, 1H), 3.72 (dt, J = 14.6, 3.4 Hz, 1H), 3.66–3.56 (m, 1H), 3.52 (d, J = 9.0 Hz, 2H), 3.04–2.88 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H).

(1R)-(1,1-dioxido-1,5,2-dithiazepan-3-yl)methyl p-tolylcarbamate (6a)

White solid, yield 93%. mp 192–193 °C. [α]D20 16.3 (c 0.40, MeOH). FTIR: 3304, 2918, 1728, 1531, 1315, 1294, 1207, 1182, 1166, 841, 746 cm⁻¹. 1H NMR (500 MHz, DMSO) δ 9.62 (s, 1H), 7.85 (d, J = 6.4 Hz, 1H), 7.34 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 8.3 Hz, 2H), 4.03 (ddd, J = 17.3, 10.9, 7.0 Hz, 2H), 3.56–3.35 (m, 3H), 3.10 (dd, J = 15.1, 4.9 Hz, 1H), 2.91 (dd, J = 15.1, 8.7 Hz, 1H), 2.86 (dd, J = 8.2, 3.8 Hz, 2H), 2.23 (s, 3H). 13C NMR (126 MHz, DMSO) δ 153.1, 136.4, 131.3, 129.1, 118.2, 65.6, 59.1, 52.4, 35.9, 27.3, 20.3. HRMS (ESI) m/z calculated for C13H18N2O4S2Na 353.0606 (M+Na)⁺, found 353.0611.

(1R)-(1,1-dioxido-1,5,2-dithiazepan-3-yl)methyl (4-fluorophenyl)carbamate (6b)

White solid, yield 66%. mp 163–164 °C. [α]D20 16.0 (c 0.40, MeOH). FTIR: 3308, 2918, 1717, 1508, 1325, 1213, 1128, 1063, 816 cm⁻¹. 1H NMR (500 MHz, Acetone) δ 8.81 (s, 1H), 7.57 (dd, J = 8.8, 4.8 Hz, 2H), 7.12–7.03 (m, 2H), 6.79 (d, J = 5.4 Hz, 1H), 4.18 (qd, J = 10.9, 6.9 Hz, 2H), 3.66–3.58 (m, 1H), 3.56–3.49 (m, 1H), 3.44 (ddd, J = 14.4, 7.2, 5.3 Hz, 1H), 3.21 (dd, J = 15.3, 5.2 Hz, 1H), 3.04 (dd, J = 15.3, 8.6 Hz, 1H), 2.96–2.91 (m, 2H). 13C NMR (126 MHz, Acetone) δ 159.2 (d, 1JCF = 239.5 Hz), 154.0, 136.2, 120.7, 115.9 (d, 2JCF = 22.5 Hz), 79.0, 66.9, 59.9, 36.7, 28.5. HRMS (ESI) m/z calculated for C12H15FN2O4S2Na 357.0355 (M+Na)⁺, found 357.0353.

General procedure for the synthesis of 7 from scaffolds 4

A solution of scaffold 4 (0.2 mmol, 1 equiv.), amine (2 mmol, 10 equiv.) and 2-hydroxypyridine (0.04 mmol, 0.2 equiv.) in toluene (1 mL) was refluxed for 14 h. The solvent was evaporated under reduced pressure and the crude product was purified via flash chromatography.
(R)-2-benzyl-N-octyl-1,5,2-dithiazepane-3-carboxamide 1,1-dioxide (7a)

White solid, yield 79%. mp 136–137 °C. [α]D20 -0.8 (c 1.00, CH2Cl2). FTIR: 3429, 2922, 2851, 1668, 1327, 1140, 1051, 854, 733, 706 cm−1. 1H NMR (500 MHz, CDCl3) δ 7.48–7.43 (m, 2H), 7.41–7.32 (m, 3H), 6.33 (s, 1H), 4.86 (d, J = 14.1 Hz, 1H), 4.22 (d, J = 14.1 Hz, 1H), 3.77–3.70 (m, 2H), 3.57 (dd, J = 15.8, 5.8 Hz, 1H), 3.47–3.35 (m, 2H), 3.01–2.93 (m, 3H), 2.88 (dt, J = 15.3, 3.5 Hz, 1H), 1.36–1.09 (m, 12H), 0.90 (t, J = 7.1 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 169.0, 135.1, 129.3, 129.1, 128.8, 64.5, 57.5, 56.1, 39.5, 37.7, 31.8, 29.1, 29.1, 29.1, 27.8, 26.6, 22.6, 14.1. HRMS (ESI) m/z calculated for C20H12N2O2S2Na 435.1752 (M+Na)+, found 435.1756.

(R)-2-benzyl-N-hexyl-1,5,2-dithiazepane-3-carboxamide 1,1-dioxide (7b)

White solid, yield 99%. mp 138–140 °C. [α]D20 -1.6 (c 0.75, CH2Cl2). FTIR: 3431, 2951, 2926, 2856, 1668, 1327, 1140, 1051, 854, 733, 706 cm−1. 1H NMR (500 MHz, CDCl3) δ 7.45 (dd, J = 7.9, 1.4 Hz, 2H), 7.42–7.35 (m, 3H), 6.33 (s, 1H), 4.86 (d, J = 14.1 Hz, 1H), 4.22 (d, J = 14.1 Hz, 1H), 3.73 (dd, J = 14.6, 8.9, 4.4 Hz, 2H), 3.57 (dd, J = 15.8, 5.8 Hz, 1H), 3.47–3.35 (m, 2H), 3.04–2.93 (m, 3H), 2.88 (dt, J = 15.4, 3.4 Hz, 1H), 1.34–1.11 (m, 8H), 0.89 (t, J = 7.2 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 169.0, 135.1, 129.3, 129.1, 128.8, 64.5, 57.5, 56.1, 39.4, 37.7, 31.4, 29.0, 27.8, 26.3, 22.5, 14.0. HRMS (ESI) m/z calculated for C16H28N2O2S2Na 407.1439 (M+Na)+, found 407.1440.

(R)-2-benzyl-N-isobutyl-1,5,2-dithiazepane-3-carboxamide 1,1-dioxide (7c)

White solid, yield 66%. mp 196–197 °C. [α]D20 -0.9 (c 1.00, CH2Cl2). FTIR: 3427, 2957, 2918, 2870, 1668, 1522, 1329, 1138, 1049, 854, 735 cm−1. 1H NMR (500 MHz, CDCl3) δ 7.48–7.43 (m, 2H), 7.42–7.33 (m, 3H), 6.42 (s, 1H), 4.85 (d, J = 14.1 Hz, 1H), 4.24 (d, J = 14.1 Hz, 1H), 3.80–3.69 (m, 2H), 3.58 (dd, J = 15.7, 5.8 Hz, 1H), 3.47–3.36 (m, 3H), 3.00 (ddd, J = 15.3, 12.6, 2.7 Hz, 1H), 2.92–2.85 (m, 2H), 2.77–2.69 (m, 1H), 1.53 (td, J = 13.4, 6.7 Hz, 1H), 0.79 (d, J = 6.7 Hz, 2H), 0.76 (d, J = 6.7 Hz, 2H). 13C NMR (126 MHz, CDCl3) δ 169.2, 135.1, 129.3, 129.2, 128.8, 64.5, 57.4, 56.0, 46.7, 37.8, 28.2, 27.8, 19.9, 19.9. HRMS (ESI) m/z calculated for C16H28N2O2S2Na 379.1126 (M+Na)+, found 379.1128.

(R)-2-(4-methoxybenzyl)-N-octyl-1,5,2-dithiazepane-3-carboxamide 1,1-dioxide (7d)

White solid, yield 59%. mp 159–160 °C. [α]D20 -0.8 (c 0.75, CH2Cl2). FTIR: 3431, 2953, 2922, 2851, 1664, 1512, 1327, 1151, 1140, 1057, 847 cm−1. 1H NMR (500 MHz, CDCl3) δ 7.39–7.34 (m, 2H), 6.92–6.86 (m, 2H), 6.32 (s, 1H), 4.80 (d, J = 14.1 Hz, 1H), 4.17 (d, J = 14.0 Hz, 1H), 3.81 (s, 3H), 3.78–3.68 (m, 2H), 3.56 (dd, J = 15.7, 5.8 Hz, 1H), 3.45–3.32 (m, 2H), 2.99 (ddd, J = 12.1, 7.4, 4.7 Hz, 3H), 2.86 (dt, J = 15.3, 3.5 Hz, 1H), 1.34–1.10 (m, 12H), 0.89 (t, J = 7.1 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 169.1, 159.9, 130.6, 127.0, 114.4, 64.4, 56.9, 56.1, 55.2, 39.5, 37.6, 31.8, 29.2, 29.1, 27.8, 26.7, 22.6, 14.1. HRMS (ESI) m/z calculated for C21H35N2O4S2 443.2038 (M+H)+, found 443.2046.

(R)-N-hexyl-2-(4-methoxybenzyl)-1,5,2-dithiazepane-3-carboxamide 1,1-dioxide (7e)

White solid, yield 50%. mp 165–166 °C. [α]D20 -1.2 (c 0.85, CH2Cl2). FTIR: 3431, 2955, 2924, 2854, 1664, 1512, 1327, 1151, 1140, 1057, 849 cm−1. 1H NMR (500 MHz, CDCl3) δ 7.38–7.34 (m, 2H), 6.92–6.87 (m, 2H), 6.32 (s, 1H), 4.80 (d, J = 14.0 Hz, 1H), 4.16 (d, J = 14.0 Hz, 1H), 3.81 (s, 3H), 3.77–3.67 (m, 2H), 3.57 (dd, J = 15.7, 5.8 Hz, 1H), 3.48–3.32 (m, 2H), 3.07–2.92 (m, 3H), 2.86 (dt, J = 15.4, 3.5 Hz, 1H), 1.36–1.10 (m, 8H), 0.88 (t, J = 7.1 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 169.1, 159.9, 130.6, 127.0, 114.4, 64.4, 56.9, 56.1, 55.2, 39.4, 37.6, 31.4, 29.1, 27.8, 26.3, 22.5, 14.0. HRMS (ESI) m/z calculated for C19H30N2O4S2Na 437.1545 (M+Na)+, found 437.1552.
**(R)-N-isobutyl-2-(4-methoxybenzyl)-1,5,2-dithiazepane-3-carboxamide 1,1-dioxide (7f)**

White solid, yield 45%. mp 175–176 °C. [α]D20 -0.7 (c 0.90, CH2Cl2). FTIR: 3427, 2955, 2926, 1664, 1514, 1327, 1153, 1140, 1126, 1057, 855, 739 cm^-1. 1H NMR (500 MHz, CDCl3) δ 7.39–7.33 (m, 2H), 6.94–6.85 (m, 2H), 6.42 (s, 1H), 4.79 (d, J = 14.0 Hz, 1H), 4.19 (d, J = 14.0 Hz, 1H), 3.81 (s, 3H), 3.76 (dd, J = 11.9, 5.9 Hz, 1H), 3.70 (dt, J = 14.7, 3.0 Hz, 1H), 3.57 (dd, J = 15.7, 5.8 Hz, 1H), 3.43 (dd, J = 15.7, 12.0 Hz, 1H), 3.37 (ddd, J = 14.6, 12.7, 3.9 Hz, 1H), 2.99 (ddd, J = 15.3, 12.7, 2.7 Hz, 1H), 2.93–2.84 (m, 2H), 2.81–2.74 (m, 1H), 1.57–1.51 (m, 1H), 0.79 (d, J = 6.7 Hz, 3H), 0.76 (d, J = 6.7 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 169.3, 159.9, 130.6, 127.0, 114.5, 64.3, 56.9, 56.0, 55.3, 46.8, 37.8, 28.2, 27.9, 19.9, 19.8. HRMS (ESI) m/z calculated for C17H26N2O4S2Na 409.1232 (M+Na)+, found 409.1221.

**Acknowledgments**

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**References**


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12. A two-step route for the synthesis of compound 3a has been previously reported, see ref 11.
Figure 1. ORTEP diagram of 3b
Scheme 1. One-pot sulfonylation and intramolecular thia-Michael protocol
Scheme 2. Reported synthesis of 1,5,2-dithiazepane 1,1-dioxide (3a)
Scheme 3. Diversification leading to 1,5,2-dithiazepane 1,1-dioxides
The synthesis of core scaffolds 3

Table 1

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$^a$Reaction time is 14 h.

$^b$Isolated yield after flash chromatography.

$^c$Microwave for 10 minutes.

$^d$Isolated yield for a 40 gram-scale reaction. The product was purified via recrystallization.