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## Application of a Double Aza-Michael Reaction in a ‘Click, Click, Cy-Click’ Strategy: From Bench to Flow

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### Abstract

The development of a ‘click, click, cy-click’ process utilizing a double aza-Michael reaction to generate functionalized 1,2,5-thiadiazepane 1,1-dioxides is reported. Optimization in flow, followed by scale out of the inter-/intramolecular double aza-Michael addition has also been realized using a microwave-assisted, continuous flow organic synthesis platform (MACOS). In addition, a facile one-pot, sequential strategy employing in situ Huisgen cycloaddition post-double aza-Michael has been accomplished, and is applicable to library synthesis.

### Keywords

double-aza-Michael; click; MACOS; flow; 1,2,5-thiadiazepane 1,1-dioxides

The development of facile, step-efficient methods to access new heterocycles is a key component in the drug-discovery process. Hetero-Michael reactions are efficient pathways that, historically, have been broadly used in synthesis, including several intramolecular examples to access a variety of heterocycles, namely, dioxolanes en route to 1,3-diols,<sup>1</sup> azacycles,<sup>2</sup> oxacycles,<sup>3</sup> thiacycles,<sup>4</sup> and bis-heterocycles.<sup>5</sup> Recently, double aza-Michael reactions have been utilized as efficient means to install two N–C bonds in a single operation.<sup>6</sup> Herein, we report a new approach termed ‘click, click, cy-click’ that utilizes two click reactions<sup>7</sup> and a double aza-Michael reaction for the facile synthesis of 1,2,5-thiadiazepane 1,1-dioxides. Optimization using a microwave-assisted continuous flow synthetic (MACOS) platform, has transformed the non-click cyclization step into a facile one-minute (resident flow time) cyclization event (cy-click) that has also been scaled out.

Although not found in nature, sultams have emerged as privileged structures due to their extensive chemical and biological profiles.<sup>8,9</sup> Recently, a number of reports of sultams have appeared demonstrating broad-spectrum bioactivity. Such reports include anti-HIV activity,<sup>10</sup> antidepressant activity,<sup>11</sup> and as inhibitors of RSV,<sup>12</sup> selective tumor necrosis factor,<sup>13</sup> and metalloproteinase.<sup>14</sup>

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Previously, the inherent reactivity of vinyl sulfonamides was utilized in a ‘click, click, cyclize’ strategy for the facile construction of diverse sultam scaffolds via intramolecular oxa- and intermolecular aza-Michael reactions (Scheme 1, pathway a).<sup>31,15</sup> At the heart of this approach is the facile production of precursor tertiary vinyl sulfonamides by the use of two click reactions,<sup>7</sup> namely, sulfonylation of in situ generated vinyl sulfonyl chloride, followed by alkylation of the resulting 2° sulfonamide and subsequent cyclization.

In this new report outlined in Scheme 1 (pathways b and c), an inter-/intramolecular double aza-Michael pathway serves as the cyclization step in a ‘click, click, cy-click’ sequence, and utilizes a TBS-protected serinol methyl ester in the initial sulfonylation step. Subsequent alkylation, followed by a one-pot,  $\beta$ -elimination/double aza-Michael reaction yields functionalized 1,2,5-thiadiazepane 1,1-dioxide scaffolds.

Overall, this facile approach utilizes the  $\beta$ -elimination of the alcohol in the serine-moiety present in **2** to generate a second Michael acceptor armed for the titled protocol. This later sequence has its roots in the biosynthesis of tryptophan, which utilizes tryptophan synthase, a pyridoxal phosphate-containing bifunctional enzyme (PLP), to catalyze an elimination/indole addition pathway on serine.<sup>16</sup> Taken collectively, the route employs two click reactions and a double aza-Michael cyclization step that is optimized using a MACOS platform<sup>17</sup> (cy-click).

Initial efforts focused on the preparation of vinyl sulfonamide **3**, obtained in a simple three-step sequence from serine methyl ester (Scheme 2). Racemic serine methyl ester was protected as a TBS-ether,<sup>18</sup> to which 2-chloroethanesulfonyl chloride was added, providing **2**, which was subsequently benzylated under mild conditions to provide **3**. A facile pathway to **5** was next envisioned to proceed via elimination of the TBS-ether moiety<sup>19,20</sup> to generate **4**, followed by a double aza-Michael reaction of an amine. Towards this goal, treatment of **3** with TBAF in tetrahydrofuran, in the absence of nucleophile, resulted in the production of elimination product **4** in 30% yield. Use of cesium carbonate in acetonitrile further promoted the elimination pathway to yield **4** in 91%. Addition of cyclopentylamine to **4** in acetonitrile gave **5** in moderate yield (Scheme 2).

Further studies showed that while **4** can be isolated, a one-pot operation consisting of adding base and cyclopentylamine to a stirring solution of **3**, directly afforded the double aza-Michael product **5a** (Table 1). Optimization of various parameters, including solvent, temperature and base (equiv), revealed that cesium carbonate in acetonitrile at 40 °C gave nice conversion (Table 1, entries 1–6). However, use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base (Table 1, entries 7–10) improved the yield significantly, with optimized conditions established using 0.1 equivalent of DBU in methanol at 40 °C for one hour (entry 10).

With the optimized conditions in hand, a demonstration set of 1,2,5-thiadiazepane 1,1-dioxides were synthesized using linear (Table 2, entries 1, 2, 5, and 6) as well as benzylamines (Table 2, entries 3, 4, and 7). Within the aliphatic amines, several linear amines worked well. Not surprisingly, more sterically encumbered *tert*-butylamine failed to undergo the double aza-Michael reaction, but instead simple Michael addition of methanol was obtained in roughly 40% yield.

In efforts to utilize the double aza-Michael strategy in library synthesis, it was deemed imperative that the scaffold be synthesized efficiently and quickly on a larger scale. This seemed achievable by combining microwave heating and flow chemistry using the MACOS (microwave-assisted, continuous-flow organic synthesis) platform. Using this synthetic technique, one set of optimization experiments is all that is necessary to obtain, and in theory, any amount of desired product can be generated by scaling the synthesis out, rather

than scaling it up, which involves extensive reaction reoptimization at each growing scale in the process.

The optimal bench conditions in Table 1 (entry 10) were initially employed in MACOS, resulting in a mixture with the mono aza-Michael product as the major component. A more complex product mixture was obtained when additional heat was applied in order to push the reaction in methanol. Use of higher-boiling *n*-butanol did provide the double aza-Michael product, but transesterification was also observed (5–15%). This problem was circumvented by the use of propan-2-ol leading to products **5a** and **5c** in 60% (0.5 g) and 71% (0.7 g), respectively (Table 2, entries 8 and 9). These proof-of-concept experiments illustrate that we can obtain any amount of product we require for library elaboration using scale-out in MACOS.

Successes with the double aza-Michael reaction led us to explore a sequential, one-pot process employing an additional in situ Huisgen 1,3-dipolar cycloaddition click reaction, to terminate the route.<sup>21</sup> The propargyl-substituted sulfonamide was synthesized in 79% yield (over three steps) using potassium carbonate in the presence of sodium iodide in *N,N*-dimethylformamide. The double aza-Michael reaction was performed using the optimal bench conditions (Table 1, entry 10), and the resultant mixture was concentrated in the reaction vial and reconstituted in dichloromethane, after which the azide and copper(I) iodide were added, and stirred at room temperature for 16 hours. Efforts aimed at simplifying the procedure by using same solvent for both double aza-Michael and Huisgen cycloaddition reactions, either gave a lower yield (in CH<sub>2</sub>Cl<sub>2</sub>) or multiple products (in MeOH). While additional efforts continue toward this goal, a set of reactions was carried out using a sequential, one-pot procedure to afford the desired products in good yields (Table 3).

In conclusion, we have developed a double aza-Michael procedure using MACOS to synthesize 1,2,5-thiadiazepane 1,1-dioxides that involves minimal chromatography and is step-efficient. Application of flow chemistry for optimization and scale-out sets the stage for library synthesis. Further investigations have led to a sequential, one-pot elimination, double aza-Michael and Huisgen cycloaddition for the synthesis of triazolated 1,2,5-thiadiazepane 1,1-dioxides. Subsequent research will be focused on library synthesis using this protocol. All compounds synthesized have been submitted to the NIH Molecular Library Small Molecule Repository (MLSMR) for distribution within the MLSCN, which will allow for extensive biological screening.

All reactions were carried out without inert atmosphere. Stirring was achieved with oven-dried magnetic stir bars. Solvents were either purchased through Sigma-Aldrich or purified by passage through the Solv-Tek purification system employing activated Al<sub>2</sub>O<sub>3</sub>.<sup>22</sup> Et<sub>3</sub>N was purified by passage over basic Al<sub>2</sub>O<sub>3</sub> or distilled over CaH<sub>2</sub> and stored over KOH. Flash column chromatography was performed with Sorbent Technologies (30930M-25, Silica Gel 60A, 40–63 μm). TLC was performed on silica gel 60F254 plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. <sup>1</sup>H, <sup>13</sup>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 a Avance AV-III 500 with a dual carbon/proton (CPDUL) cryoprobe operating at 500 MHz, 125 MHz, respectively. High-resolution mass spectrometry (HRMS) measurements were obtained on a VG Instrument ZAB double-focusing mass spectrometer.

## Generation of 1,2,5-Thiadiazepane 1,1-Dioxides 5 via Double Aza-Michael on Bench; General Procedure

To the tertiary sulfonamide **3** (0.2 mmol, 1 equiv) was added MeOH (0.1 M), amine (0.22 mmol, 1.1 equiv), and DBU (0.04 mmol, 0.2 equiv). The solution was stirred at 40 °C for 1 h, the solvent was evaporated and the crude product was purified by flash column chromatography on silica gel (hexane–EtOAc, 3:1).

### Methyl 5-Cyclopentyl-2-(4-methylbenzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (5a)

Yield: 57 mg (75%); colorless oil.

FTIR (thin film): 2951, 2866, 1734, 1329, 1142  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.29 (d,  $J$  = 8.0 Hz, 2 H), 7.15 (d,  $J$  = 7.8 Hz, 2 H), 4.79 (d,  $J$  = 15.0 Hz, 1 H), 4.31 (d,  $J$  = 15.0 Hz, 1 H), 3.94–3.86 (m, 1 H), 3.60 (s, 3 H), 3.45 (s, 1 H), 3.43 (d,  $J$  = 3.3 Hz, 1 H), 3.23 (d,  $J$  = 4.3 Hz, 1 H), 3.22 (d,  $J$  = 4.1 Hz, 1 H), 3.11 (ddd,  $J$  = 14.8, 4.1, 4.1 Hz, 1 H), 3.01 (ddd,  $J$  = 14.7, 6.7, 6.7 Hz, 1 H), 2.76–2.67 (m, 1 H), 2.35 (s, 3 H), 1.67 (m, 4 H), 1.48–1.38 (m, 2 H), 1.35–1.20 (m, 2 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 170.6, 137.8, 132.8, 129.2, 129.0, 63.3, 57.0, 55.0, 54.6, 53.6, 52.3, 48.7, 30.8, 30.2, 23.6, 23.5, 21.1.

HRMS (TOF MS ES<sup>+</sup>):  $m/z$  calcd for  $\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}_4\text{S}$  ( $\text{M} + \text{H}$ )<sup>+</sup>: 381.1848; found: 381.1851.

### Methyl 2-(4-Methoxybenzyl)-5-octyl-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (5b)

Yield: 57 mg (65%); colorless oil.

FTIR (thin film): 2951, 2928, 2854, 1736, 1514, 1329, 1248, 1142  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.34–7.29 (m, 2 H), 6.90–6.84 (m, 2 H), 4.67 (d,  $J$  = 14.9 Hz, 1 H), 4.34 (d,  $J$  = 14.9 Hz, 1 H), 3.90 (dd,  $J$  = 10.5, 6.5 Hz, 1 H), 3.81 (s, 3 H), 3.57 (s, 3 H), 3.47 (dd,  $J$  = 14.7, 10.6 Hz, 1 H), 3.36 (dd,  $J$  = 14.7, 6.5 Hz, 1 H), 3.26–3.22 (m, 2 H), 3.02 (dd,  $J$  = 7.8, 3.9 Hz, 2 H), 2.46–2.40 (m, 2 H), 1.41–1.17 (m, 12 H), 0.90 (t,  $J$  = 7.0 Hz, 3 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 170.5, 159.4, 130.4, 127.8, 113.8, 57.1, 55.8, 55.3, 55.3, 54.8, 53.3, 52.3, 50.0, 31.8, 29.4, 29.3, 27.7, 27.1, 22.7, 14.1.

HRMS (TOF MS ES<sup>+</sup>):  $m/z$  calcd for  $\text{C}_{22}\text{H}_{37}\text{N}_2\text{O}_5\text{S}$  ( $\text{M} + \text{H}$ )<sup>+</sup>: 441.2423; found: 441.2419.

### Methyl 2-Benzyl-5-butyl-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (5c)

Yield: 53 mg (74%); light yellow solid; mp 58 °C.

FTIR (thin film): 2954, 2931, 2869, 1737, 1454, 1330, 1143, 1072, 744, 703  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.38–7.36 (m, 2 H), 7.32–7.27 (m, 3 H), 4.72 (d,  $J$  = 15.3 Hz, 1 H), 4.32 (d,  $J$  = 15.0 Hz, 1 H), 3.93 (m, 1 H), 3.49 (s, 3 H), 3.43–3.27 (m, 2 H), 3.22–3.20 (m, 2 H), 2.99 (m, 2 H), 2.44 (t,  $J$  = 7.2 Hz, 2 H), 1.37–1.32 (m, 2 H), 1.26–1.21 (m, 2 H), 0.89 (t,  $J$  = 7.2 Hz, 3 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.3, 135.9, 128.9, 128.4, 127.9, 57.4, 55.8, 55.2, 54.7, 53.7, 52.1, 49.3, 29.8, 20.1, 13.9$ .

HRMS (TOF MS ES<sup>+</sup>):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_4\text{S}$  (M)<sup>+</sup>: 354.1613; found: 354.1606.

### **Methyl 2-Benzyl-5-(4-fluorobenzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (5d)**

Yield: 56 mg (69%); yellow oil.

FTIR (thin film): 2951, 2843, 1732, 1508, 1329, 1219, 1142, 771, 743, 704  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.44\text{--}7.35$  (m, 5 H), 7.10–7.05 (m, 2 H), 7.02–6.94 (m, 2 H), 4.94 (d,  $J = 15.1$  Hz, 1 H), 4.32 (d,  $J = 15.1$  Hz, 1 H), 3.86 (dd,  $J = 10.5, 6.6$  Hz, 1 H), 3.59–3.55 (m, 1 H), 3.57 (s, 3 H), 3.52–3.46 (m, 2 H), 3.34 (dd,  $J = 14.7, 6.6$  Hz, 1 H), 3.25–3.22 (m, 2 H), 3.04–2.96 (m, 2 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.2, 162.1$  (d,  $^1J_{\text{C,F}} = 245.9$  Hz), 135.9, 133.7 (d,  $^4J_{\text{C,F}} = 3.1$  Hz), 129.9 (d,  $^3J_{\text{C,F}} = 8.0$  Hz), 129.3, 128.7, 128.2, 115.4 (d,  $^2J_{\text{C,F}} = 21.3$  Hz), 59.1, 57.1, 55.7, 55.1, 53.6, 52.3, 49.7.

HRMS (TOF MS ES<sup>+</sup>):  $m/z$  calcd for  $\text{C}_{20}\text{H}_{24}\text{FN}_2\text{O}_4\text{S}$  (M + H)<sup>+</sup>: 407.1441; found: 407.1438.

### **Methyl 2-(4-Chlorobenzyl)-5-(4-methoxybenzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (5e)**

Yield: 74 mg (82%); yellow oil.

FTIR (thin film): 2951, 2932, 2837, 1736, 1610, 1512, 1329, 1246, 1144, 1078, 1014, 837, 741  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.36$  (s, 4 H), 7.10 (d,  $J = 8.6$  Hz, 2 H), 6.86 (d,  $J = 8.7$  Hz, 2 H), 4.77 (d,  $J = 15.3$  Hz, 1 H), 4.36 (d,  $J = 15.3$  Hz, 1 H), 3.88 (dd,  $J = 10.4, 6.7$  Hz, 1 H), 3.82 (s, 3 H), 3.66 (d,  $J = 12.4$  Hz, 1 H), 3.58 (d,  $J = 13.0$  Hz, 1 H), 3.53 (s, 3 H), 3.45 (dd,  $J = 14.4, 10.5$  Hz, 1 H), 3.32 (dd,  $J = 14.5, 6.6$  Hz, 1 H), 3.25–3.14 (m, 2 H), 3.03–2.90 (m, 2 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.0, 159.0, 134.6, 133.9, 130.4, 130.0, 129.7, 128.7, 113.9, 60.6, 57.7, 55.9, 55.3, 54.8, 52.9, 52.3, 49.5$ .

HRMS (TOF MS ES<sup>+</sup>):  $m/z$  calcd for  $\text{C}_{21}\text{H}_{26}\text{ClN}_2\text{O}_5\text{S}$  (M + H)<sup>+</sup>: 453.1251; found: 453.1242.

### **Methyl 2-(4-Chlorobenzyl)-5-phenethyl-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (5f)**

Yield: 67 mg (77%); yellow oil.

FTIR (thin film): 2951, 2930, 2847, 1738, 1491, 1331, 1142, 1082, 1014, 752, 739, 700  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.36\text{--}7.30$  (m, 2 H), 7.30–7.22 (m, 5 H), 7.19–7.14 (m, 2 H), 4.31 (d,  $J = 15.4$  Hz, 1 H), 4.23 (d,  $J = 15.4$  Hz, 1 H), 3.91 (dd,  $J = 10.5, 6.7$  Hz, 1 H),

3.51 (s, 3 H), 3.48 (dd,  $J = 14.5, 10.6$  Hz, 1 H), 3.39 (dd,  $J = 14.5, 6.7$  Hz, 1 H), 3.24–3.19 (m, 2 H), 3.12–2.99 (m, 2 H), 2.95–2.83 (m, 2 H), 2.81–2.73 (m, 2 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.0, 139.4, 134.5, 133.7, 130.2, 128.6, 128.6, 128.5, 126.4, 58.2, 57.9, 56.2, 54.3, 52.9, 52.3, 49.9, 34.4$ .

HRMS (TOF MS ES+):  $m/z$  calcd for  $\text{C}_{21}\text{H}_{26}\text{ClN}_2\text{O}_4\text{S}$  ( $\text{M} + \text{H}$ ) $^+$ : 437.1302; found: 437.1281.

### Methyl 2-(4-Fluorobenzyl)-5-isobutyl-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (5g)

Yield: 48 mg (65%); colorless oil.

FTIR (thin film): 2955, 2870, 1738, 1510, 1329, 1221, 1146, 1078, 754  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.62\text{--}7.32$  (m, 2 H), 7.19–6.91 (m, 2 H), 4.69 (d,  $J = 15.1$  Hz, 1 H), 4.38 (d,  $J = 15.1$  Hz, 1 H), 3.92 (dd,  $J = 10.6, 6.5$  Hz, 1 H), 3.55 (s, 3 H), 3.48 (dd,  $J = 14.7, 10.7$  Hz, 1 H), 3.33 (dd,  $J = 14.7, 6.5$  Hz, 1 H), 3.28–3.22 (m, 2 H), 3.04–2.99 (m, 2 H), 2.28–2.18 (m, 2 H), 1.68–1.62 (m, 1 H), 0.86 (d,  $J = 6.6$  Hz, 6 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.2, 162.5$  (d,  $^1J_{\text{C,F}} = 246.7$  Hz), 131.8 (d,  $^4J_{\text{C,F}} = 3.2$  Hz), 130.7 (d,  $^3J_{\text{C,F}} = 8.2$  Hz), 115.4 (d,  $^2J_{\text{C,F}} = 21.5$  Hz), 63.9, 57.4, 56.5, 54.9, 53.0, 52.3, 50.4, 26.8, 20.5, 20.5.

HRMS (TOF MS ES+):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{26}\text{FN}_2\text{O}_4\text{S}$  ( $\text{M} + \text{H}$ ) $^+$ : 373.1597; found: 373.1595.

### Methyl 5-Benzyl-2-[4-(trifluoromethyl)benzyl]-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (5h)

Yield: 72 mg (79%); yellow oil.

FTIR (thin film): 2953, 2930, 2843, 1740, 1325, 1163, 1144, 1122, 1067, 735, 700  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.64$  (d,  $J = 8.1$  Hz, 2 H), 7.56 (d,  $J = 8.1$  Hz, 2 H), 7.36–7.28 (m, 3 H), 7.25–7.21 (m, 2 H), 4.85 (d,  $J = 15.6$  Hz, 1 H), 4.47 (d,  $J = 15.6$  Hz, 1 H), 3.95 (dd,  $J = 10.4, 6.6$  Hz, 1 H), 3.77 (d,  $J = 13.2$  Hz, 1 H), 3.69 (d,  $J = 13.2$  Hz, 1 H), 3.50 (s, 3 H), 3.49 (dd,  $J = 14.4, 10.5$  Hz, 1 H), 3.35 (dd,  $J = 14.4, 6.6$  Hz, 1 H), 3.29–3.19 (m, 2 H), 3.08–2.94 (m, 2 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 169.8, 140.3, 138.0, 130.2$  (q,  $^2J_{\text{C,F}} = 32.5$  Hz), 129.1, 128.6, 128.5, 127.8, 126.2 (q,  $^1J_{\text{C,F}} = 272.1$  Hz), 125.4 (q,  $^3J_{\text{C,F}} = 3.7$  Hz), 61.6, 58.0, 56.1, 54.7, 52.9, 52.3, 49.7.

HRMS (TOF MS ES+):  $m/z$  calcd for  $\text{C}_{21}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_4\text{S}$  ( $\text{M} + \text{H}$ ) $^+$ : 457.1409; found: 457.1406.

### Scale-Out Synthesis of 1,2,5-Thiadiazepane 1,1-Dioxides 5a and 5c Utilizing MACOS Flow Platform; General Procedure

A stock solution containing the respective sulfonamide **3a**, **3c** (2.4 or 2.8 mmol, 1.0 equiv), DBU (2.4 or 2.8 mmol, 1.0 equiv), and amine (2.8 or 3.3 mmol, 1.2 equiv) in *i*-PrOH (0.3 M) was prepared and loaded into Hamilton gas-tight syringe (10 mL). The tubing was

primed with *i*-PrOH and the syringe was connected to the reactor system with the aid of Microtight™ fittings. A sealed collection vial was connected to the system, where a pressurized airline (75 psi) was attached to create backpressure. A Harvard 22 syringe pump was set to deliver the reaction solution at a rate of 75  $\mu$ L/min. The single mode microwave was programmed to heat constantly with the power level controlled manually so as to keep the temperature constant at the specified levels (130 W,  $\sim$ 100  $^{\circ}$ C). The effluent from the reactor was fed into a sealed vial and analyzed directly by  $^1$ H NMR spectroscopy immediately after the reaction. The crude reaction mixture was collected and the product was purified by flash chromatography (EtOAc–*n*-pentane, 2:8) to afford the desired sultam **5a** (534 mg, 60%, greenish oil) and **5c** (700 mg, 71%, light yellow solid).

### Triazolated 1,2,5-Thiadiazepane 1,1-Dioxides **7**; General Procedure

To the tertiary sulfonamide **6** (0.2 mmol, 1 equiv) was added MeOH (0.1 M), amine (0.24 mmol, 1.2 equiv), and DBU (0.04 mmol, 0.2 equiv). The solution was stirred at 40  $^{\circ}$ C for 1 h. The solvent was removed under a Techne sample concentrator. The residue was further dried under high vacuum pump for 2 h. To the residue was added  $\text{CH}_2\text{Cl}_2$  (0.1 M), azide (0.4 mmol, 2 equiv), CuI (0.04 mmol, 0.2 equiv) and stirred overnight. The solvent was removed under a Techne sample concentrator and the crude product was purified by flash column chromatography on silica gel (hexane–EtOAc, 2:1).

#### Methyl 5-Butyl-2-{[1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (**7a**)

Yield: 45 mg (61%); yellow oil.

FTIR (thin film): 2953, 2930, 1747, 1329, 1144, 779, 758  $\text{cm}^{-1}$ .

$^1$ H NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.61 (s, 1 H), 7.18 (s, 4 H), 5.47 (s, 2 H), 4.74 (d,  $J$  = 15.9 Hz, 1 H), 4.50 (d,  $J$  = 15.9 Hz, 1 H), 4.08 (t,  $J$  = 8.5 Hz, 1 H), 3.54 (s, 3 H), 3.43 (d,  $J$  = 8.6 Hz, 2 H), 3.24–3.13 (m, 2 H), 3.07–2.93 (m, 2 H), 2.52–2.39 (m, 2 H), 2.35 (s, 3 H), 1.43–1.33 (m, 2 H), 1.33–1.20 (m, 2 H), 0.91 (t,  $J$  = 7.2 Hz, 3 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 170.3, 144.2, 138.7, 131.5, 129.8, 128.1, 123.2, 58.2, 55.8, 54.7, 54.4, 54.0, 52.2, 49.8, 45.7, 29.8, 21.1, 20.2, 13.9.

HRMS (TOF MS ES<sup>+</sup>):  $m/z$  calcd for  $\text{C}_{21}\text{H}_{32}\text{N}_5\text{O}_4\text{S}$  (M + H)<sup>+</sup>: 450.2175; found: 450.2160.

#### Methyl 5-Butyl-2-{[1-(3-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (**7b**)

Yield: 51 mg (65%); colorless oil.

FTIR (thin film): 2953, 2860, 1745, 1327, 1143, 775  $\text{cm}^{-1}$ .

$^1$ H NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.70 (s, 1 H), 7.37–7.29 (m, 2 H), 7.25 (s, 1 H), 7.18–7.15 (m, 1 H), 5.50 (s, 2 H), 4.73 (d,  $J$  = 15.9 Hz, 1 H), 4.54 (d,  $J$  = 15.9 Hz, 1 H), 4.11 (t,  $J$  = 8.5 Hz, 1 H), 3.57 (s, 3 H), 3.46–3.40 (m, 2 H), 3.19 (t,  $J$  = 5.2 Hz, 2 H), 3.05–2.96 (m, 2 H), 2.56–2.43 (m, 2 H), 1.46–1.35 (m, 2 H), 1.34–1.22 (m, 2 H), 0.92 (t,  $J$  = 7.3 Hz, 3 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 170.2, 144.7, 136.6, 135.0, 130.4, 129.0, 128.0, 126.0, 123.5, 58.5, 55.8, 54.9, 54.4, 53.5, 52.3, 49.8, 45.8, 29.8, 20.2, 14.0.

HRMS (TOF MS ES<sup>+</sup>): *m/z* calcd for C<sub>20</sub>H<sub>29</sub>ClN<sub>5</sub>O<sub>4</sub>S (M + H)<sup>+</sup>: 470.1629; found: 470.1630.

### Methyl 2-[[1-(2-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl]methyl]-5-butyl-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (7c)

Yield: 63 mg (73%); yellow oil.

FTIR (thin film): 2953, 2930, 2860, 1747, 1329, 1144, 756 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.73 (s, 1 H), 7.62 (dd, *J* = 7.9, 1.1 Hz, 1 H), 7.32 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.24 (td, *J* = 7.8, 1.8 Hz, 1 H), 7.18 (dd, *J* = 7.6, 1.5 Hz, 1 H), 5.66 (s, 2 H), 4.78 (d, *J* = 15.9 Hz, 1 H), 4.52 (d, *J* = 15.9 Hz, 1 H), 4.11 (t, *J* = 8.5 Hz, 1 H), 3.59 (s, 3 H), 3.44 (d, *J* = 8.6 Hz, 2 H), 3.26–3.14 (m, 2 H), 3.00 (dt, *J* = 9.1, 3.3 Hz, 2 H), 2.53–2.36 (m, 2 H), 1.43–1.33 (m, 2 H), 1.30–1.20 (m, 2 H), 0.90 (t, *J* = 7.3 Hz, 3 H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ = 170.3, 144.1, 134.0, 133.3, 130.5, 130.4, 128.3, 123.7, 123.5, 58.3, 55.8, 54.7, 54.5, 53.9, 52.4, 49.9, 45.6, 29.8, 20.2, 14.0.

HRMS (TOF MS ES<sup>+</sup>): *m/z* calcd for C<sub>20</sub>H<sub>29</sub>BrN<sub>5</sub>O<sub>4</sub>S (M + H)<sup>+</sup>: 514.1124; found: 514.1134.

### Methyl 5-Benzyl-2-[[1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl]methyl]-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (7d)

Yield: 67 mg (83%); yellow oil.

FTIR (thin film): 2951, 2924, 1745, 1329, 1142, 735 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.61 (s, 1H), 7.36–7.28 (m, 3H), 7.23 (d, *J* = 7.0 Hz, 2H), 7.20–7.12 (m, 4H), 5.50 (s, 2H), 4.89 (d, *J* = 15.9 Hz, 1H), 4.49 (d, *J* = 15.9 Hz, 1H), 4.08 (dd, *J* = 10.1, 6.9 Hz, 1H), 3.67 (d, *J* = 13.4 Hz, 1H), 3.59 (d, *J* = 13.4 Hz, 1H), 3.54 (s, 3H), 3.50 (dd, *J* = 14.7, 10.1 Hz, 1H), 3.44 (dd, *J* = 14.7, 6.9 Hz, 1H), 3.24–3.09 (m, 2H), 3.05–2.90 (m, 2H), 2.34 (s, 3H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ = 170.2, 144.1, 138.8, 138.0, 131.5, 129.8, 128.6, 128.5, 128.1, 127.6, 123.2, 59.2, 58.1, 55.9, 54.5, 54.1, 52.3, 49.1, 45.5, 21.1.

HRMS (TOF MS ES<sup>+</sup>): *m/z* calcd for C<sub>24</sub>H<sub>29</sub>N<sub>5</sub>O<sub>4</sub>S + Na (M + Na)<sup>+</sup>: 506.1838; found: 506.1838.

### Methyl 5-Benzyl-2-[[1-(3-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl]methyl]-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (7e)

Yield: 55 mg (65%); colorless oil.

FTIR (thin film): 2951, 2833, 1747, 1327, 1142, 737 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.70 (s, 1 H), 7.38–7.24 (m, 8 H), 7.16 (d, *J* = 7.1 Hz, 1 H), 5.52 (s, 2 H), 4.88 (d, *J* = 16.0 Hz, 1 H), 4.54 (d, *J* = 15.9 Hz, 1 H), 4.11 (dd, *J* = 10.1, 7.0 Hz, 1 H), 3.72 (d, *J* = 13.3 Hz, 1 H), 3.64 (d, *J* = 13.5 Hz, 1 H), 3.56 (s, 3 H), 3.51 (dd, *J* = 14.9, 10.2 Hz, 1 H), 3.45 (dd, *J* = 14.7, 7.0 Hz, 1 H), 3.23–3.12 (m, 2 H), 3.05–2.94 (m, 2 H).



$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 170.1, 144.6, 138.0, 136.5, 135.1, 130.4, 129.0, 128.6, 128.5, 128.0, 127.6, 126.0, 123.5, 59.5, 58.5, 56.0, 54.4, 53.5, 52.4, 49.2, 45.6.

HRMS (TOF MS ES+):  $m/z$  calcd for  $\text{C}_{23}\text{H}_{26}\text{ClN}_5\text{O}_4\text{S} + \text{Na}$  ( $\text{M} + \text{Na}$ ) $^+$ : 526.1292; found: 526.1281.

### **Methyl 5-Benzyl-2-[[1-(2-bromobenzyl)-1H-1,2,3-triazol-4-yl]methyl]-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (7f)**

Yield: 69 mg (74%); yellow oil.

FTIR (thin film): 2951, 2841, 1744, 1329, 1142, 737  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.74 (s, 1 H), 7.62 (d,  $J$  = 7.8 Hz, 1 H), 7.32 (m, 4 H), 7.25–7.17 (m, 4 H), 5.69 (s, 2 H), 4.93 (d,  $J$  = 15.9 Hz, 1 H), 4.52 (d,  $J$  = 15.9 Hz, 1 H), 4.11 (dd,  $J$  = 10.1, 6.9 Hz, 1 H), 3.67 (d,  $J$  = 13.4 Hz, 1 H), 3.60 (d,  $J$  = 13.4 Hz, 1 H), 3.59 (s, 3 H), 3.52 (dd,  $J$  = 14.8, 10.2 Hz, 1 H), 3.46 (dd,  $J$  = 14.9, 7.1 Hz, 1 H), 3.26–3.11 (m, 2 H), 3.06–2.92 (m, 2 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 170.2, 144.0, 138.0, 133.9, 133.3, 130.5, 130.4, 128.6, 128.5, 128.2, 127.6, 123.7, 123.5, 59.1, 58.2, 55.9, 54.6, 54.0, 52.4, 49.2, 45.4.

HRMS (TOF MS ES+):  $m/z$  calcd for  $\text{C}_{23}\text{H}_{26}\text{BrN}_5\text{O}_4\text{S} + \text{Na}$  ( $\text{M} + \text{Na}$ ) $^+$ : 570.0787; found: 570.0790.

### **Methyl 5-(2-Hydroxyethyl)-2-[[1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl]methyl]-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (7g)**

Yield: 58 mg (81%); yellow oil.

FTIR (thin film): 3381, 2951, 2926, 1740, 1329, 1142, 779, 758  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz, acetone- $d_6$ ):  $\delta$  = 8.00 (s, 1 H), 7.27 (d,  $J$  = 7.7 Hz, 2 H), 7.19 (d,  $J$  = 7.6 Hz, 2 H), 5.57 (s, 2 H), 4.85 (d,  $J$  = 15.9 Hz, 1 H), 4.44 (d,  $J$  = 16.0 Hz, 1 H), 4.17 (dd,  $J$  = 10.4, 6.9 Hz, 1 H), 3.53 (s, 3 H), 3.50–3.28 (m, 6 H), 3.19–3.04 (m, 2 H), 3.04–2.92 (m, 1 H), 2.52 (s, 2 H), 2.31 (s, 3 H).

$^{13}\text{C}$  NMR (126 MHz, acetone- $d_6$ ):  $\delta$  = 171.2, 144.5, 138.8, 134.0, 130.2, 128.9, 124.6, 60.7, 58.1, 57.3, 57.1, 55.4, 54.0, 52.2, 51.2, 45.8, 21.0.

HRMS (TOF MS ES+):  $m/z$  calcd for  $\text{C}_{19}\text{H}_{27}\text{N}_5\text{O}_5\text{S} + \text{Na}$  ( $\text{M} + \text{Na}$ ) $^+$ : 460.1631; found: 460.1632.

### **Methyl 2-[[1-(3-Chlorobenzyl)-1H-1,2,3-triazol-4-yl]methyl]-5-(2-hydroxyethyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (7h)**

Yield: 66 mg (87%); yellow oil.

FTIR (thin film): 3433, 2951, 2928, 1742, 1329, 1142, 777  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz, acetone- $d_6$ ):  $\delta$  = 8.12 (s, 1 H), 7.45–7.30 (m, 4 H), 5.67 (s, 2 H), 4.86 (d,  $J$  = 16.0 Hz, 1 H), 4.47 (d,  $J$  = 16.0 Hz, 1 H), 4.20 (dd,  $J$  = 10.4, 7.0 Hz, 1 H), 3.56 (s, 3 H), 3.52–3.42 (m, 4 H), 3.40–3.32 (m, 1 H), 3.20–3.05 (m, 2 H), 3.03–2.94 (m, 1 H), 2.56 (t,  $J$  = 4.8 Hz, 2 H), 2.09 (s, 1 H).

$^{13}\text{C}$  NMR (126 MHz, acetone- $d_6$ ):  $\delta$  = 171.2, 144.7, 139.3, 134.9, 131.4, 129.1, 128.8, 127.4, 125.0, 60.7, 58.3, 57.5, 57.1, 55.4, 53.4, 52.2, 51.2, 45.8.

HRMS (TOF MS ES+):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{24}\text{ClN}_5\text{O}_5\text{S} + \text{Na}$  ( $\text{M} + \text{Na}$ ) $^+$ : 480.1084; found: 480.1088.

### Methyl 2-[[1-(2-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl]methyl]-5-(2-hydroxyethyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-Dioxide (7i)

Yield: 62 mg (73%); yellow oil.

FTIR (thin film): 3385, 2926, 2930, 1734, 1327, 1142, 760  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz, acetone- $d_6$ ):  $\delta$  = 8.08 (s, 1 H), 7.68 (d,  $J$  = 8.5 Hz, 1 H), 7.41 (t,  $J$  = 7.4 Hz, 1 H), 7.32 (dd,  $J$  = 10.4, 4.7 Hz, 1 H), 7.22 (d,  $J$  = 7.5 Hz, 1 H), 5.74 (s, 2 H), 4.89 (d,  $J$  = 16.0 Hz, 1 H), 4.48 (d,  $J$  = 15.9 Hz, 1 H), 4.26–4.15 (m, 1 H), 3.59 (s, 3 H), 3.56–3.35 (m, 6 H), 3.18–3.09 (m, 2 H), 3.03–2.96 (m, 1 H), 2.56 (s, 2 H).

$^{13}\text{C}$  NMR (126 MHz, acetone- $d_6$ ):  $\delta$  = 171.2, 136.0, 133.9, 131.2, 131.2, 129.6, 129.1, 125.2, 123.8, 60.7, 58.2, 57.4, 57.1, 55.4, 54.1, 52.3, 51.2, 45.8.

HRMS (TOF MS ES+):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{24}\text{BrN}_5\text{O}_5\text{S} + \text{Na}$  ( $\text{M} + \text{Na}$ ) $^+$ : 524.0579; found: 524.0587.

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

### Acknowledgments

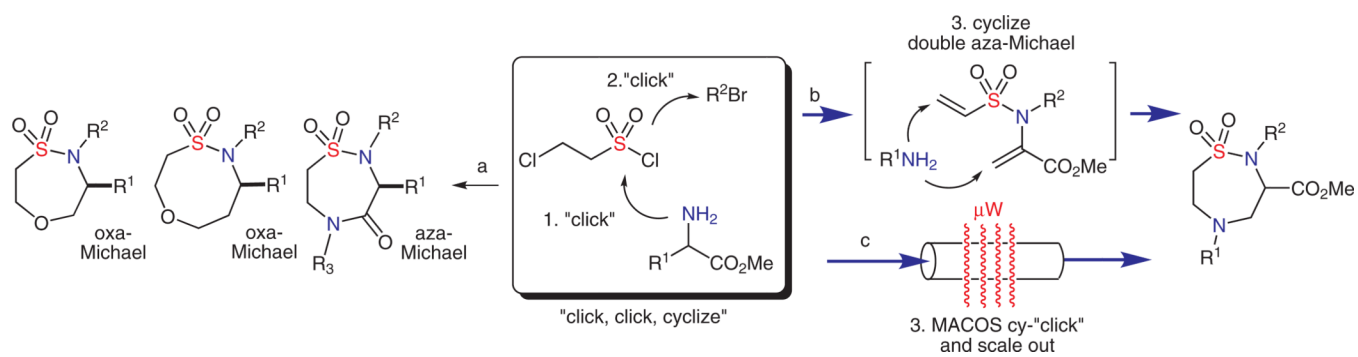
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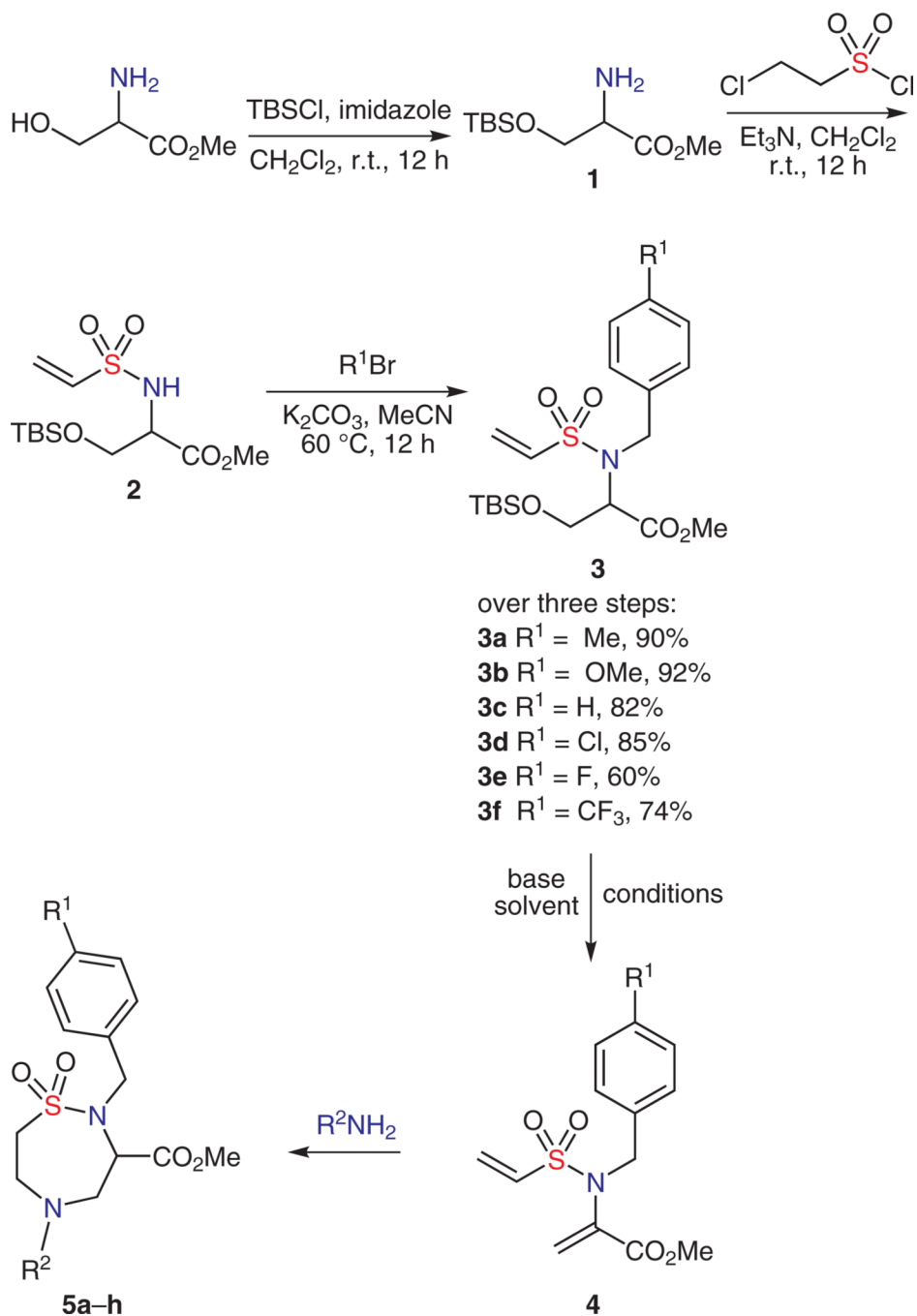
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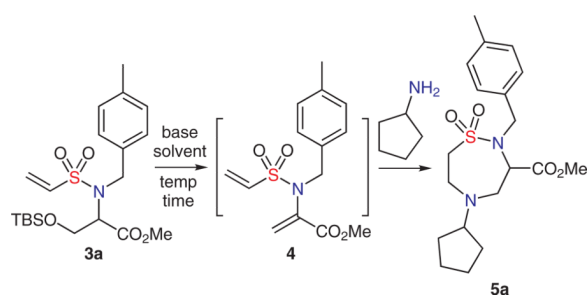
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**Scheme 1.**  
Hetero-Michael pathways using a 'click, click, cyclize' strategy



**Scheme 2.**  
The preparation of double aza-Michael precursors

**Table 1**Optimization of One-Pot Elimination and Double Aza-Michael Reaction<sup>a</sup>

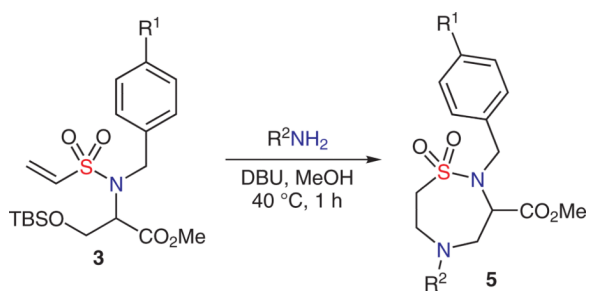
Entry	Base	Temp, time	Solvent	Yield (%) <sup>b</sup>
1	Cs <sub>2</sub> CO <sub>3</sub> (1 equiv)	40 °C, 12 h	MeCN	50
2	Cs <sub>2</sub> CO <sub>3</sub> (1 equiv)	40 °C, 12 h	CH <sub>2</sub> Cl <sub>2</sub>	44
3	Cs <sub>2</sub> CO <sub>3</sub> (1 equiv)	40 °C, 12 h	MeOH	0
4	Cs <sub>2</sub> CO <sub>3</sub> (1 equiv)	60 °C, 12 h	MeCN	43
5	Cs <sub>2</sub> CO <sub>3</sub> (2 equiv)	60 °C, 12 h	MeCN	32
6	Cs <sub>2</sub> CO <sub>3</sub> (1 equiv)	40 °C, 12 h	DMF	42
7	DBU (0.5 equiv)	r.t., 12 h	MeCN	23
8	DBU (0.1 equiv)	40 °C, 1 h	DMF	30
9	DBU (0.1 equiv)	r.t., 12 h	MeOH	69
10	DBU (0.1 equiv)	40 °C, 1 h	MeOH	75

<sup>a</sup> A solution of compound **3a** (1 equiv) and cyclopentylamine (1.1 equiv) in solvent (0.1 M) was added base and stirred at the indicated temperature and time.

<sup>b</sup> Isolated yields following silica gel chromatography.

Table 2

Synthesis of 1,2,5-Thiadiazepane 1,1-Dioxides



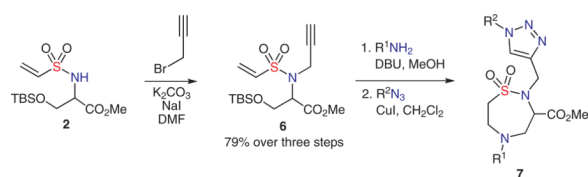
Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Yield (%)
1	MeO	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	<b>5b</b>	65
2	H	<i>n</i> -Bu	<b>5c</b>	74
3	H	4-FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>5d</b>	69
4	Cl	4-MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>5e</b>	82
5	Cl	PhCH <sub>2</sub> CH <sub>2</sub>	<b>5f</b>	77
6	F	<i>i</i> -Bu	<b>5g</b>	65
7	CF <sub>3</sub>	Bn	<b>5h</b>	79
8 <sup>a</sup>	Me	<i>c</i> -C <sub>5</sub> H <sub>9</sub>	<b>5a<sup>a</sup></b>	60 <sup>a</sup>
9 <sup>a</sup>	H	<i>n</i> -Bu	<b>5c<sup>a</sup></b>	71 <sup>a</sup>

<sup>a</sup>Performed using the following MACOS conditions: **3a/3c** (1.0 equiv), DBU (1.0 equiv), amine (1.2 equiv), *i*-PrOH (0.3 M), 75 μL/min, 100 °C, 130 W.



**Table 3**

Sequential, One-Pot Elimination, Double Aza-Michael and Huisgen 1,3-Dipolar Cycloaddition



Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Yield (%)
1	<i>n</i> -Bu	4-MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>7a</b>	61
2	<i>n</i> -Bu	3-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>7b</b>	65
3	<i>n</i> -Bu	2-BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>7c</b>	73
4	Bn	4-MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>7d</b>	83
5	Bn	3-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>7e</b>	65
6	Bn	2-BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>7f</b>	74
7	HOCH <sub>2</sub> CH <sub>2</sub>	4-MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>7g</b>	81
8	HOCH <sub>2</sub> CH <sub>2</sub>	3-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>7h</b>	87
9	HOCH <sub>2</sub> CH <sub>2</sub>	2-BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>7i</b>	73