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Multicapillary Flow Reactor: Synthesis of 1,2,5-Thiadiazepane 1,1-Dioxide Library Utilizing One-Pot Elimination and Inter-/Intramolecular Double aza-Michael Addition Via Microwave-Assisted, Continuous-Flow Organic Synthesis (MACOS)

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Abstract

A microwave-assisted, continuous-flow organic synthesis (MACOS) protocol for the synthesis of functionalized 1,2,5-thiadiazepane 1,1-dioxide library, utilizing a one-pot elimination and inter-/intramolecular double aza-Michael addition strategy is reported. The optimized protocol in MACOS was utilized for scale-out and further extended for library production using a multicapillary flow reactor. A 50-member library of 1,2,5-thiadiazepane 1,1-dioxides was prepared on a 100- to 300-mg scale with overall yields between 50 and 80% and over 90 % purity determined by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy.

Keywords

double aza-Michael; MACOS; 1,2,5-thiadiazepane 1,1-dioxide library; sultams

1. Introduction

Diversity-oriented synthesis (DOS) is an emerging field involving the synthesis of combinatorial libraries of diverse small molecules for biological screening [1]. In contrast to target-oriented synthesis that prepares a specific target compound, DOS is used to prepare collections of structurally complex and diverse compounds from simple starting materials, typically through the use of “split-pool” combinatorial chemistry [2]. DOS is used by researchers in the pharmaceutical, agrochemical, and biotechnology industries to reduce the time and cost associated with producing effective biologically active compounds.

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Supporting Information Available

Supplementary data (^{1}H- and ^{13}C-NMR spectra) associated with this article can be found on the journal's homepage at www.akademiai.com

Sultams are useful heterocycles for medicinal chemistry applications, and a number has demonstrated significant biological activity [3]. Methods that have been used to prepare these cyclic sulfonamides include the intramolecular Diels–Alder reaction [4], cyclization of aminosulfonyl chlorides [5], cycloadditions [6], radical cyclization [7], transition metal-catalyzed approaches [8], and ring-closing metathesis (RCM) [9]. Moreover, we have developed a variety of methodologies for the generation of five to eight-membered annulated and non-annulated sultams through processes we have termed “Click-Click-Cyclize” [10], “Click-Cyclize” [11], reagent-based DOS [12], “Click, Click, Cy-Click” [13], and Heck, aza-Michael (HaM) strategies [14,15].

Our continued interest in the development of new methodologies to synthesize various sultams libraries for high through put screening (HTS) [10–15] has prompted us to investigate flow technology for parallel synthesis of functionalized 1,2,5-thiadiazepane 1,1-dioxide scaffolds utilizing a microwave-assisted continuous-flow organic synthesis (MACOS) platform. Previously, we reported on the MACOS preparation of 1,2,5-thiadiazepane 1,1-dioxides and their scale-up [13]. Herein, we report the full details with the production of a 50-member library utilizing multicapillary flow reactors (Scheme 1).

2. Results and Discussion

Inspired by our recently reported batch one-pot elimination/double aza-Michael (DaM) strategy for the preparation of 1,2,5-thiadiazepane 1,1-dioxides [13], we decided to apply a one-pot elimination and DaM strategy in MACOS to generate the desired scaffold efficiently using a parallel multicapillary flow reactor.

Initial efforts focused on the preparation of a suitable Michael acceptor for the DaM reaction. Towards this goal, racemic serine methyl ester (**1**) was protected with a *tert*-butyldimethylsilyl (TBS) group [16] to provide a latent Michael acceptor, which would become activated by the *in situ* β-elimination of the *tert*-butyldimethylsilyl hydroxide group in the DaM step (Table 1). A “click” sulfonylation on **2** with commercially available 2-chloroethanesulfonyl chloride provided secondary sulfonamide **3**; the second Michael accepting moiety was formed following β-elimination of HCl. DaM precursor **4** was prepared after benzylation of **3** under mild conditions (Scheme 2). Utilizing this 3-step protocol a collection of building blocks of tertiary vinyl sulfonamides on multigram scale was assembled in excellent yield 75–90% with a variety of electron rich and poor benzyl substituents (Scheme 2).

After successful preparation of the DaM building blocks, the next task was to optimize the DaM reaction in MACOS for the scale-out preparation of these target molecules. As a starting point, the best batch conditions were selected and applied in MACOS (Table 1, Entry 1), which led to a mixture of DaM and mono aza-Michael (MaM) products. Heating to a higher temperature in an effort to convert MaM products to DaM products led to a complicated mixture. When DMF solvent was used with *t*BuOK as a base (flow rate 50 μL/min at 150 °C), a complex mixture was produced in which there was no desired product detected (Table 1, Entry 2). When the reaction was performed at 100 °C to avoid decomposition, still, no desired product was observed (Table 1, Entry 3). We examined the base and found that Et_3N in DMF was ineffective leading only to starting material recovery (Table 1, Entry 4). Use of DBU, which has intermediate basicity between *t*BuOK and Et_3N, provided the DaM product in 30% yield in DMF after screening a variety of parameters, namely flow rate, power, and temperature (Table 1, Entries 5–9). In THF (Table 1, Entry 16), aza-Michael cyclization of the initially-formed Michael intermediate was curtailed owing to the formation of the double addition product resulting from the intermolecular addition of the secondary amine of this intermediate into a second molecule of **4**. Similar

reactivity was observed in MACOS studies on the intramolecular aza-Michael cyclization to isoindolines [15]. When *n*BuOH was used as a solvent, the target DaMproducts were produced, but they were always accompanied by transesterification products (Table 1, Entry 12). In an attempt to mitigate this side reaction, a 1:1 mixture of *n*BuOH and MeOH was used, but this led to the same product mixture (Table 1, Entry 13). The transesterification problem was ultimately overcome by switching solvent from *n*BuOH to *i*PrOH, which provided the desired product in 55% yield (Table 1, Entry 14).

After the process was tested on a few examples at the milligram scale using the optimized protocol (Table 1, Entry 14), we then set out to expand the scope of this reaction and scale-out the quantity of the sultam products. This DaM MACOS strategy afforded the desired sultams in excellent yields on gram scale, and the process could be run as long as desired to make virtually any quantity [13]. With these results in hand, a parallel MACOS capillary reactor was used to further streamline library synthesis. A variety of primary amines, including linear, cyclic, and benzyl amine derivatives was chosen for the DaM reaction to generate a 50-member library of 1,2,5-thiadiazepane 1,1-dioxides (Scheme 3, Figure 1).

3. Conclusion

We have developed a sequential elimination, double aza-Michael (DaM) cyclization protocol in MACOS for the synthesis of 1,2,5-thiadiazepane 1,1-dioxides. This process readily produces large quantities of product using a scale-out approach. Alternatively use of a parallel MACOS capillary reactor facilitated the streamlined preparation of a 50-member sultam library. This collection took approximately 2 weeks to complete, including purification, and yielded 100–300 mg quantities of each product. These compounds have been submitted to the NIH Molecular Library Small Molecule Repository (MLSMR) for distribution within the MLSCN, which will allow for extensive biological screening.

4. Experimental

4.1. Microwave Irradiation Experiments

All MACOS experiments were performed in 1700 μm (ID) borosilicate capillaries, using a single mode Biotage initiator operating at a frequency of 2.45 GHz with irradiation power from 0 to 350 W. The capillary was fed reactants from Hamilton gastight syringes attached to a Harvard 22 syringe pump pre-set to the desired flow rate. The system was connected to a sealed collection vial, where a pressurized airline (75 psi) was attached to create back-pressure. The temperatures reported were measured off the surface of the capillaries by the IR sensor built into the microwave chamber. All reagents and solvents were purchased from commercial sources and used without additional purification. Column chromatography purifications were carried out using the flash technique on silica gel 60 (200–400 mesh). ^{1}H- and carbon nuclear magnetic resonance (^{13}C-NMR) spectroscopy was run using a Bruker Advance 400 MHz (400 MHz and 100 MHz, respectively). All ^{1}H-NMR spectra were calibrated to the signal from the residual proton of the deuterated chloroform solvent (7.26 ppm) while ^{13}C-NMR spectra were calibrated to the middle carbon signal of the triplet for deuterated chloroform (77.00 ppm). All compounds in this study have been isolated by silica gel chromatography for the purpose of spectroscopic identification and to verify yield.

4.2. General Procedure: Synthesis of Sulfonamides 5A–5 F Utilizing MACOS Flow-Platform

At a time, four stock solutions containing the sulfonamide **4** (1.0 equiv.), DBU (1.2 equiv.), and a different amine (1.2 equiv.) in *i*PrOH, (0.2–0.3 M) were prepared and loaded into four Hamilton gastight syringes (3 mL). The tubing was primed with *i*PrOH, and the syringes were connected to the reactor system with the aid of Microtight™ fittings. AHarvard 22

syringe pumpwas set to deliver the reaction solution at a rate of 75 μL/min. These reactions mixtures were simultaneously irradiated and collected in separate sealed vials. After completion of the reaction, the internal pressure of the system was released by piercing the septum with the needle after which the septum was removed and crude product was analyzed directly by ^{1}H-NMR spectroscopy. The solvent was removed from the reaction mixture in vacuum by rotavap, and the crude products were purified directly by flash column chromatography on silica gel (n-Pentane/EtOAc = 8:2) to afford products **5A–5F** in 50–80% yield with over 90% purity determined by ^{1}H-NMR spectroscopy.

4.2.1. Methyl 5-(cyclohexylmethyl)-2-(4-methylbenzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5Aa)—Utilizing the general procedure, sultam **5Aa** was isolated in 76% yield (217 mg, 0.53 mmol) as a colorless solid; Mp 45–47 °C; Fourier transform infrared spectrometry (FTIR) (thin film): 2923, 2847, 1745, 1453, 1325, 1134, 1067, 1005, 864, 762 cm^{-1}; ^{1}H NMR (300 MHz $CDCl_3$) δ 7.27 (d, *J*=8.1 Hz, 2 H), 7.14 (d, *J*=7.8 Hz, 2 H), 4.79 (d, *J*=15.0 Hz, 1 H), 4.25 (d, *J*=15.0, Hz, 1 H) 3.91 (dd, *J*=10.5, 6.6 Hz, 1 H), 3.57 (s, 3 H), 3.50 (dd, *J*=15.2, 10.5 Hz, 1 H), 3.56 (dd, *J*=6.9, 6.6 Hz, 1 H), 3.26–3.21 (m, 2 H), 3.01–2.96 (m, 2 H), 2.32 (s, 3 H), 2.16 (d, *J*=7.2 Hz, 2 H), 1.67–1.59 (m, 5 H), 1.28–1.14 (m, 4 H), 0.77 (m, 2 H) ppm; ^{13}C NMR (75 MHz $CDCl_3$) δ 170.5, 137.7, 132.7, 129.2, 129.1, 61.6, 56.8, 56.5, 55.0, 53.4, 52.2, 50.4, 36.1, 31.3, 31.3, 26.6, 25.9, 25.6, 21.1 ppm; HRMS (ESI): calculated for $C_{21}H_{33}N_2O_4S$ (M+H): 409.2161; found 409.2161.

4.2.2. Methyl 5-(4-chlorobenzyl)-2-(4-methylbenzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5Ab)—Utilizing the general procedure, sultam **5Ab** was isolated in 54% yield (164 mg, 0.38 mmol) as a colorless liquid; FTIR (thin film): 2949, 2918, 2838, 1739, 1321, 1138, 1085, 1009, 764 cm^{-1}; ^{1}H NMR (300 MHz $CDCl_3$) δ 7.32–7.21 (m, 6 H), 7.04 (d, *J*=8.4 Hz, 2 H), 4.94 (d, *J*=15.0 Hz, 1 H) 4.23 (d, *J*=15.0 Hz, 1 H), 3.86–3.81 (dd, *J*=10.5, 6.9 Hz, 1 H), 3.59 (s, 3 H), 3.53 (d, *J*=10.5, Hz, 2 H), 3.48 (d, *J*=10.2, Hz, 1 H), 3.37 (dd, *J*=14.7, 6.9 Hz, 1 H), 3.25–321 (m, 2 H), 3.02–2.98 (m, 2 H), 2.39 (s, 3 H) ppm; ^{13}C NMR (75 MHz $CDCl_3$) δ 170.2, 138.0, 136.6, 133.1, 132.8, 129.6, 129.4, 128.6, 58.8, 56.7, 55.7, 55.1, 53.3, 52.3, 49.8 21.2 ppm; high resolution mass spectrometry (HRMS) [electrospray ionization (ESI)] calculated for $C_{21}H_{26}ClN_2O_4S$ (M+H) 437.1302; found 437.1301.

4.2.3. Methyl 2-benzyl-5-(4-chlorobenzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5Ba)—Utilizing the general procedure, sultam **5Ba** was isolated in 54% yield (166 mg, 0.39 mmol) as a colorless solid; Mp 89–91 °C; FTIR (thin film) 2949, 2927, 2838, 1734, 1481, 1450, 1330, 1147, 1071, 1014, 773 cm^{-1}; ^{1}H NMR (300 MHz $CDCl_3$) δ 7.44 (m, 5 H), 7.28 (d, *J*=8.4 Hz, 2 H), 7.06 (d, *J*=8.4 Hz, 2 H), 4.97 (d, *J*=15.0 Hz, 1 H), 4.30 (d, *J*=15.0 Hz, 1 H), 3.89 (dd, *J*=10.5, 6.6 Hz, 1 H), 3.57 (s, 3 H), 3.55–3.45 (m, 3 H), 3.37 (dd, *J*=14.7, 6.9 Hz, 1 H), 3.26 (m, 2 H), 3.02–2.98 (m, 2 H) ppm; ^{13}C NMR (75 MHz $CDCl_3$) δ 170.1, 136.6, 135.9, 133.2, 129.7, 129.3, 128.7, 128.2, 59.1, 57.0, 55.7, 55.1, 53.6, 52.3, 49.8 ppm; HRMS (ESI) calculated for $C_{22}H_{24}ClN_2O_4S$ (M+H) 423.1145; found 423.1142.

4.2.4. Methyl 2-benzyl-5-(cyclohexylmethyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5Bb)—Utilizing the general procedure, sultam **5Bb** was isolated in 56% yield (160 mg, 0.41 mmol) as a colorless crystalline solid; Mp 52–54 °C. FTIR (thin film): 2923, 2847, 1743, 1450, 1325, 1138, 1067, 1000, 867, 742 cm^{-1}; ^{1}H NMR (300 MHz $CDCl_3$) δ 7.41–7.29 (m, 5 H), 4.82 (d, *J*=15.3 Hz, 1 H), 4.33 (d, *J*=15.0 Hz, 1 H), 3.96 (dd, *J*=10.5, 6.6 Hz, 1 H), 3.56 (s, 3 H), 3.48–3.43 (m, 1 H), 3.36–3.24 (m, 3 H), 3.03–2.99 (m, 2 H), 2.23 (d, *J*=6.9 Hz, 2 H), 1.68 (m, 5 H), 1.34–1.16 (m, 4 H), 0.84–0.76 (m, 2 H) ppm. ^{13}C NMR (75 MHz $CDCl_3$) δ 170.4, 135.9, 129.1, 128.5, 128.0, 62.2, 57.1, 56.6, 55.0, 53.6, 52.2, 50.4,

36.2, 31.4, 31.3, 26.6, 25.9; HRMS (ESI) calculated for $C_{20}H_{31}N_2O_4S$ (M+H) 395.2005; found 395.2003.

4.2.5. Methyl 2-(4-fluorobenzyl)-5-(4-methoxybenzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5Ca)—Utilizing the general procedure, sultam **5Ca** was isolated in 52% yield (132 mg, 0.30 mmol) as a colorless solid; Mp 59–61 °C; FTIR (thin film) 2954, 2914, 2834, 1734, 1601, 1512, 1321, 1245, 1134, 1080 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.24–7.38 (m, 2 H), 7.14–7.04 (m, 4 H), 6.88 (d, *J*=8.7 Hz, 2 H), 4.80 (d, *J*=15.3 Hz, 1 H), 4.36 (d, *J*=15.3 Hz, 1 H), 3.93 (dd, *J*=10.5, 6.9 Hz, 1 H), 3.82 (s, 3 H), 3.69 (dd, *J*=12.9, 25.5 Hz, 2 H), 3.52 (s, 3 H), 3.47 (d, *J*=10.5 Hz, 1 H), 3.37 (dd, *J*=14.4, 6.6 Hz, 1 H), 3.23 (m, 2 H), 3.01 (m, 2 H) ppm; ^{13}C NMR (75 MHz $CDCl_3$) δ 170.0, 164.1 (d, *J*=245.3 Hz), 159.1, 131.8 (d, *J*=3.0 Hz), 130.9 (d, *J*=8.3 Hz), 130.1 (d, *J*=27.0 Hz), 115.5 (d, *J*=21.7 Hz), 113.9, 60.4, 57.6, 55.8, 55.2, 54.8, 52.9, 52.2, 49.5 ppm; HRMS (ESI) calculated for $C_{21}H_{26}FN_2O_5S$ (M +H) 437.1546; found 437.1545.

4.2.6. Methyl 5-(cyclohexylmethyl)-2-(4-fluorobenzyl)-1,2-thiazepane-3-carboxylate 1,1-dioxide (5Cb)—Utilizing the general procedure, sultam **5Cb** was isolated in 56% yield (134 mg, 0.33 mmol) as a colorless solid; Mp 57–59 °C; FTIR (thin film) 2927, 2847, 1739, 1597, 1508, 1450, 1321, 1218, 1138, 1005, 760 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.39 (dd, *J*=8.4, 5.4 Hz, 2 H), 7.05 (dd, *J*=8.7, 8.7 Hz, 2 H), 4.72 (d, *J*=15.3 Hz, 1 H), 4.34 (d, *J*=15.0 Hz, 1 H), 3.95 (dd, *J*=10.5, 6.9 Hz, 1 H), 3.55 (s, 3 H), 3.51 (dd, *J*=14.7, 10.5 Hz, 1 H), 3.35 (dd, *J*=14.7, 6.6 Hz, 1 H), 3.28 (m, 2 H), 3.02 (m, 2 H), 2.29 (d, *J*=7.2 Hz, 2 H), 1.70 (br d, *J*=3.6 Hz, 5 H), 1.34–1.14 (m, 4 H), 0.86 (m, 2 H) ppm; ^{13}C NMR (75 MHz $CDCl_3$) δ 170.2, 164.1 (d, *J*=245.3 Hz), 131.8 (d, *J*=3.0 Hz), 130.8 (d, *J*=8.3 Hz), 115.5 (d, *J*=21.8 Hz), 62.9, 57.4, 56.7, 54.9, 52.9, 52.2, 50.4, 36.4, 31.5, 31.4, 26.6, 25.9 ppm; HRMS (ESI): calculated for $C_{20}H_{29}FN_2O_4S$ 412.1832; 412.1830.

4.2.7. Methyl 2-(4-bromobenzyl)-5-(4-bromophenethyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5 Da)—Utilizing the general procedure, sultam **5 Da** was isolated in 51% yield (172 mg, 0.31 mmol) as a colorless liquid; FTIR (thin film) 2927, 2842, 1734, 1489, 1329, 1138, 1066, 1004, 761 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.46 (dd, *J*=8.4, 2.4 Hz, 4 H), 7.23 (d, *J*=8.1 Hz, 2 H), 7.05 (d, *J*=8.1 Hz, 2 H), 4.37 (d, *J*=15.3 Hz, 1 H), 4.33 (d, *J*=15.3 Hz, 1 H), 3.91 (dd, *J*=10.2, 6.9 Hz, 1 H), 3.54 (s, 3 H), 3.47–3.39 (m, 2 H), 3.24 (m, 2 H), 3.07 (m, 2 H), 2.86–2.81 (m, 2 H), 2.73 (d, *J*=6.9 Hz, 2 H) ppm; ^{13}C NMR (75 MHz $CDCl_3$) δ 169.9, 138.4, 135.0, 131.6, 131.5, 130.4, 130.3, 121.9, 120.1, 57.9, 57.8, 56.2, 54.3, 53.1, 52.3, 50.0, 33.7 ppm; HRMS (ESI): calculated for $C_{21}H_{25}Br_2N_2O_4S$ (M+H) 561.3072; found 561.3061.

4.2.8. Methyl 2-(4-bromobenzyl)-5-(cyclohexylmethyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5Db)—Utilizing the general procedure, sultam **5Db** was isolated in 63% yield (180 mg, 0.38 mmol) as a colorless liquid; FTIR (thin film) 2927, 2847, 1752, 1494, 1450, 1325, 1258, 1143, 1071, 1009, 760 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.47 (d, *J*=8.4 Hz, 2 H), 7.29 (d, *J*=8.4 Hz, 2 H), 4.70 (d, *J*=15.3 Hz, 1 H), 4.30 (d, *J*=15.3 Hz, 1 H), 3.94 (dd, *J*=10.5, 6.6 Hz, 1 H), 3.55 (s, 3 H), 3.48 (dd, *J*=14.7, 10.5 Hz, 1 H), 3.34 (dd, *J*=14.7, 6.6 Hz, 1 H), 3.29 (m, 2 H), 3.00 (m, 2 H), 2.28 (d, *J*=6.9 Hz, 2 H), 1.69 (m, 5 H), 1.36–1.16 (m, 4 H), 0.86 (m, 2 H) ppm; ^{13}C NMR (75 MHz $CDCl_3$) δ 170.1, 135.1, 131.6, 130.6, 121.9, 63.0, 57.6, 56.7, 54.8, 53.0, 52.3, 50.4, 36.3, 31.5, 31.4, 26.6, 25.9 ppm; HRMS (ESI): calculated for $C_{20}H_{30}BrN_2O_4S$ (M+H) 473.1110; found 473.1109.

4.2.9. Methyl 5-(cyclohexylmethyl)-2-(3-(methoxycarbonyl)benzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5Ea)—Utilizing the general procedure, sultam **5Ea** was isolated in 64% yield (184 mg, 0.41 mmol) as a colorless liquid; FTIR (thin

film) 2923, 2847, 1730, 1445, 1330, 1285, 1209, 1014, 740 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.98 (d, *J*=1.5 Hz, 2 H), 7.94 (m, 1 H), 7.64 (t, *J*=7.8 Hz, 1 H), 4.76- (d, *J*=15.3 Hz, 1 H), 4.30 (d, *J*=15.3 Hz, 1 H), 3.93 (m, 1 H), 3.90 (s, 3 H), 3.52 (s, 3 H), 3.48 (dd, *J*=14.7, 10.5 Hz, 1 H), 3.34 (dd, *J* =14.7, 6.9 Hz, 1 H), 3.26 (m, 2 H), 3.00 (m, 2 H), 2.28 (m, 2 H), 1.66 (m, 5 H), 1.34–1.08 (m, 4 H), .82–0.75 (m, 2 H) ppm; ^{13}C NMR (75 MHz $CDCl_3$) δ 170.1, 166.6, 136.5, 133.6, 130.3, 129.7, 129.2, 128.6, 62.6, 57.5, 56.6, 54.8, 53.4, 52.2, 52.2, 50.4, 36.3, 31.4, 31.3, 26.6, 25.9, 25.8 ppm; HRMS (ESI) calculated for $C_{22}H_{33}N_2O_6S$ (M+H) 453.2059; found 453.2057.

4.2.10. Methyl 5-(4-chlorobenzyl)-2-(3-(methoxycarbonyl)benzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5Eb)—Utilizing the general procedure, sultam **5Eb** was isolated in 57% yield (174 mg, 0.36 mmol) as a colorless liquid; FTIR (thin film) 2963, 2927, 2851, 1726, 1427, 1334, 1289, 1209, 1143, 1009, 738 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 8.05 (d, *J* =8.4 Hz, 2 H), 7.70 (d, *J*=7.8 Hz, 1 H), 7.51 (t, *J*=7.8 Hz, 1 H), 7.29 (d, *J*=8.4 Hz, 2 H), 7.12 (d, *J*=8.4 Hz, 2 H), 4.90 (d, *J*=15.3 Hz, 1 H), 4.48 (d, *J*=15.3 Hz, 1 H), 3.95 (s, 3 H), 3.87 (dd, *J*=10.5, 6.9 Hz, 1 H), 3.68 (d, *J*=7.8 Hz, 2 H), 3.54 (s, 3 H), 3.51 (dd, *J*=14.4, 10.5 Hz, 1 H), 3.36 (dd, *J*=14.7, 6.6 Hz, 1 H), 3.25 (m, 2 H), 3.02 (m, 2 H) ppm; ^{13}C NMR (75 MHz $CDCl_3$) δ 169.9, 166.6, 136.6, 136.5, 133.7, 133.3, 130.5, 129.9, 129.7, 129.3, 128.8, 128.7, 60.1, 57.6, 56.0, 54.7, 53.4, 52.3, 49.9 ppm; HRMS (ESI) calculated for $C_{22}H_{26}ClN_2O_6S$ (M+H) 481.1200; found 481.1180.

4.2.11. Methyl 2-(3-cyanobenzyl)-5-(cyclohexylmethyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5Fa)—Utilizing the general procedure, sultam **5Fa** was isolated in 63% yield (180 mg, 0.43 mmol) as a colorless liquid; FTIR (thin film) 2923, 2851, 1752, 1454, 1338, 1267, 1143, 1005, 760 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.72 (d, *J*=6.0 Hz, 2 H), 7.62 (d, *J*=7.5 Hz, 1 H), 7.50 (m, 1 H), 4.71 (d, *J*=15.9 Hz, 1 H), 4.44 (d, *J*=15.6 Hz, 1 H), 4.03 (dd, *J*=10.2, 6.6 Hz, 1 H), 3.55 (s, 3 H), 3.49 (dd, *J*=14.4, 10.5 Hz, 1 H), 3.35 (d, *J*=6.6 Hz, 1 H), 3.29 (m, 2 H), 3.03 (m, 2 H), 2.39 (m, 2 H), 1.77 (m, 5 H), 1.39–1.18 (m, 4 H), 0.91–0.85 (m, 2 H) ppm; ^{13}C NMR (75MHz $CDCl_3$) δ 169.8, 138.0, 133.1, 132.0, 131.5, 129.3, 118.5, 112.5, 63.9, 58.2, 56.8, 54.7, 52.8, 52.3, 50.3, 36.5, 33.5, 31.6, 31.4, 26.6, 25.9 ppm; HRMS (ESI) calculated for $C_{21}H_{30}N_3O_4S$ (M+H) 420.1957; found 420.1956.

4.2.12. Methyl 5-benzyl-2-(3-cyanobenzyl)-1,2,5-thiadiazepane-3-carboxylate 1,1-dioxide (5Fb)—Utilizing the general procedure, sultam **5Fb** was isolated in 57% yield (160 mg, 0.39 mmol) as a colorless liquid; FTIR (thin film) 2949, 2927, 2838, 1748, 1427, 1334, 1138, 1076, 1005, 747, 702 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 7.72 (d, *J*=7.5 Hz, 2 H), 7.63 (d, *J*=7.8 Hz, 1 H), 7.51 (dd, *J*=7.5, 8.1 Hz, 1 H), 7.40–7.27 (m, 5 H), 4.76 (d, *J*=15.9 Hz, 1 H), 4.46 (d, *J*=15.6 Hz, 1 H), 3.99 (dd, *J*=10.2, 6.9 Hz, 1 H), 3.83 (q, *J*=13.2 Hz, 2 H), 3.51 (s, 3 H), 4.71 (d, *J*=10.5 Hz, 1 H), 3.38 (dd, *J*=14.1, 6.9 Hz, 1 H), 3.26 (m, 2 H), 3.09–2.98 (m, 2 H) ppm; ^{13}C NMR (75 MHz $CDCl_3$) δ 169.6, 138.0, 138.0, 133.1, 132.0, 131.5, 129.3, 128.7, 128.6, 127.8, 118.5, 112.5, 61.9, 58.3, 56.1, 54.5, 52.7, 52.3, 49.6 ppm; HRMS (ESI) calculated for $C_{21}H_{24}N_3O_4S$ (M+H) 414.1488; found 414.1487.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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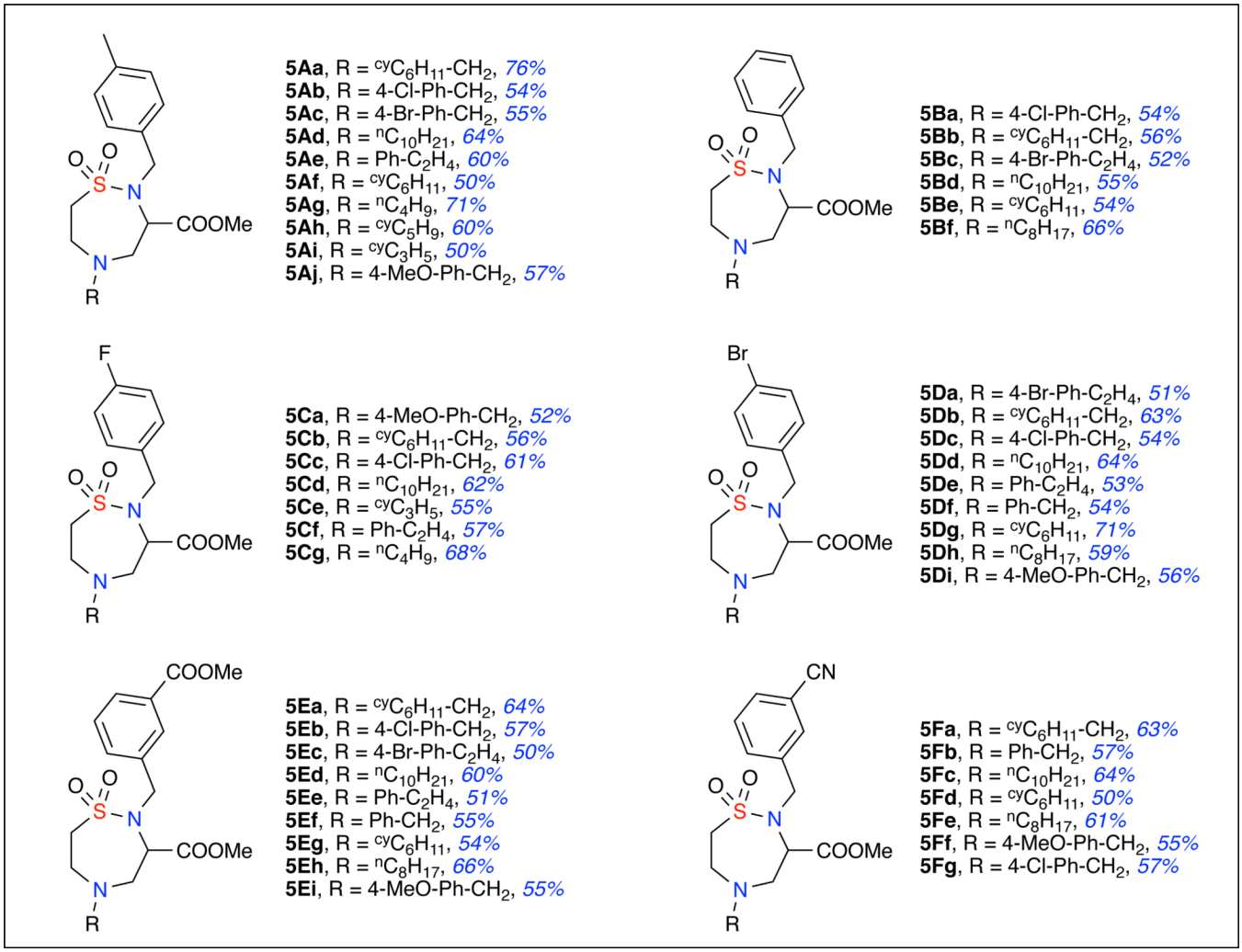
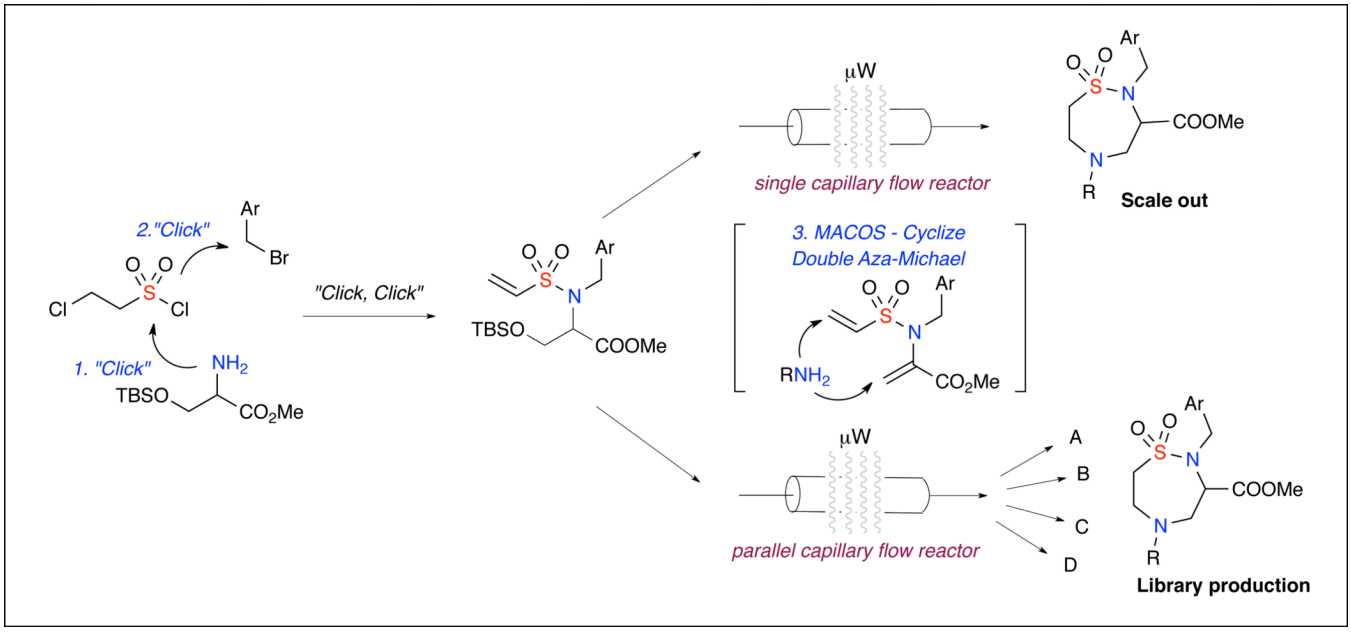
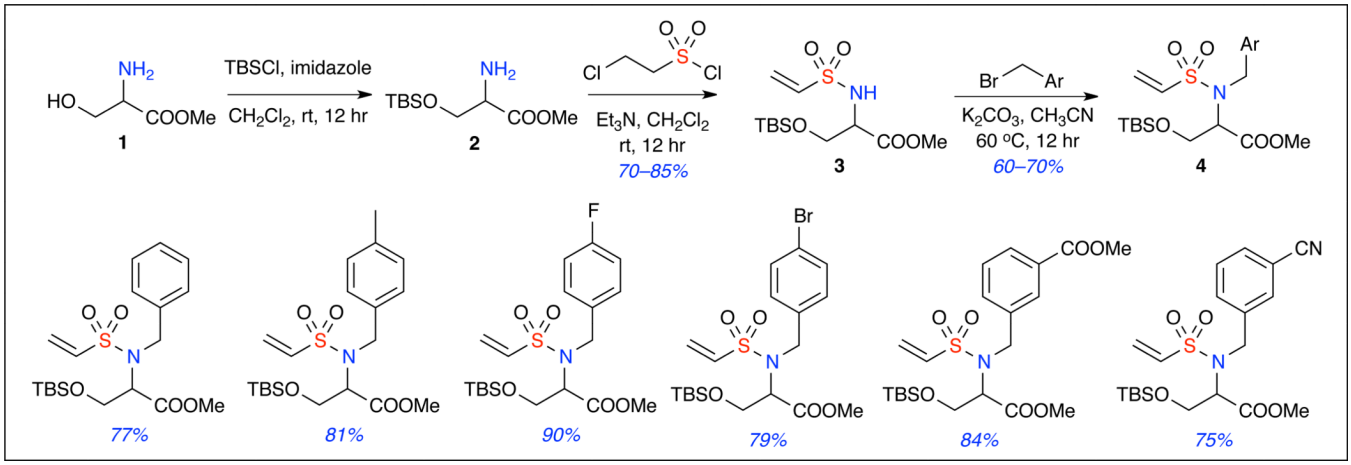


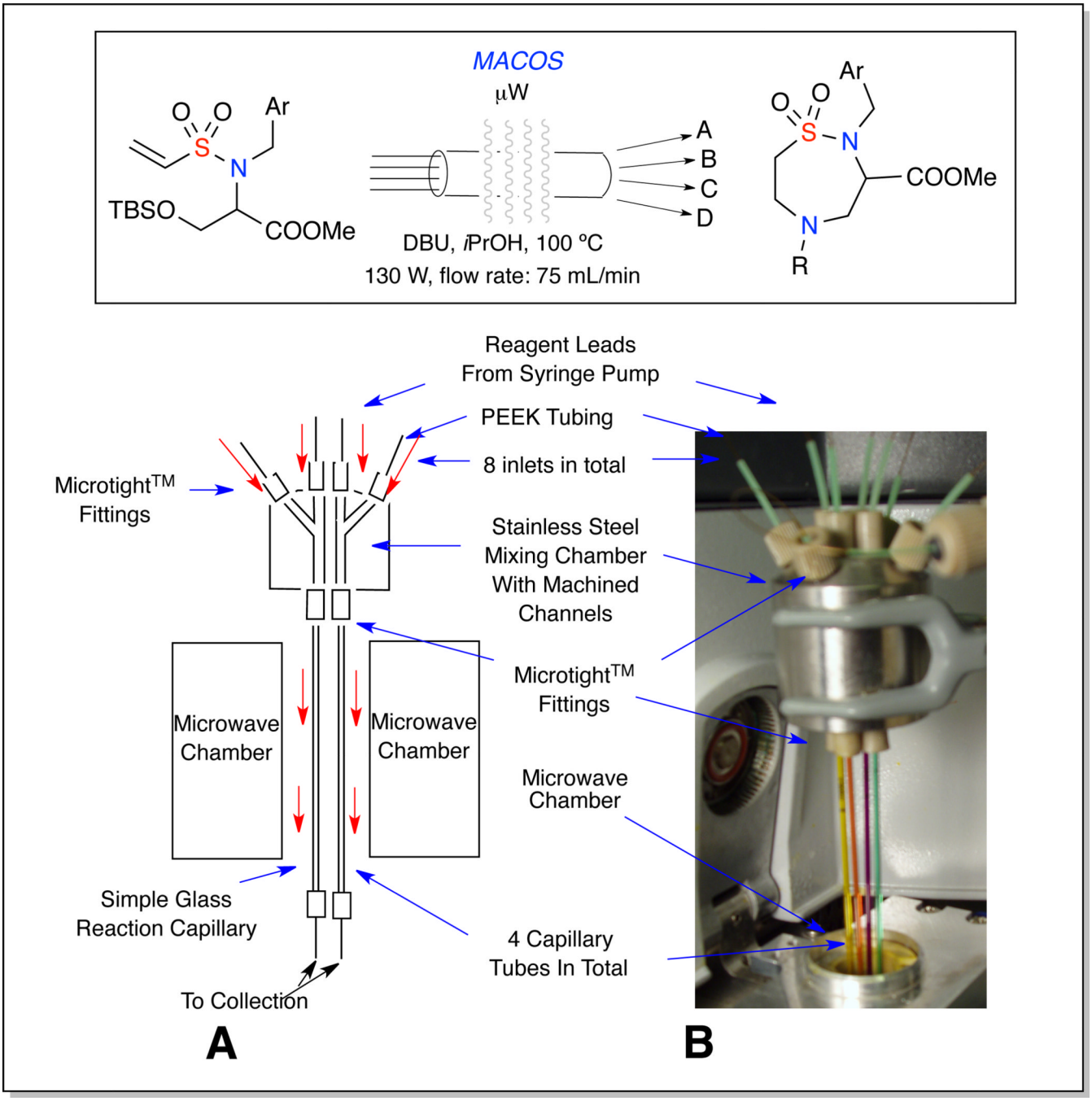
Figure 1.
1,2,5-thiadiazepane 1,1-dioxide library via MACOS



Scheme 1.
One-pot elimination and double aza-Michael (DaM) strategy in flow



Scheme 2.
Preparation of double aza-Michael precursors



Scheme 3.

Synthesis of 1,2,5-thiadiazepane 1,1-dioxide library via MACOS using multi-capillary flow reactor. (A) Schematic of the parallel, capillary multireactor system. (B) Photograph of the parallel, capillary multireactor system

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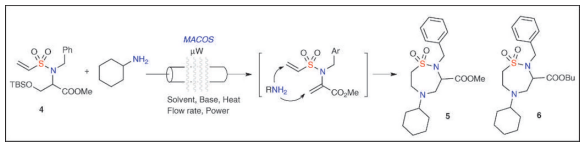
Table 1

Optimization of the elimination/double aza-Michael reaction sequence in MACOS[a]



Entry	Solvent	Base	Flow rate (μL/min)	Temp.(°C)	Power (w)	Yield %[b]
1	MeOH	DBU	70	100	80	Mixture
2	DMF	*t*BuOK	50	150	200	–
3	DMF	*t*BuOK	50	100	100	–
4	DMF	Et_3N	50	120	150	–
5	DMF	DBU	30	170	250	Traces
6	DMF	DBU	50	160	250	8
7	DMF	DBU	70	130	150	15
8	DMF	DBU	70	110	100	22
9	DMF	DBU	70	100	80	30
10	CH_3CN	DBU	70	95	100	20
11	DMF	DBU	50	150	200	–
12	*n*BuOH	DBU	50	100	80	45
13	*n*BuOH MeOH (1:1)	DBU	70	100	80	40
14	*i*PrOH	DBU	70	90	60	55
15	*i*PrOH	DBU	70	75	30	38
16	THF	DBU	70	75	100	–

[a]A solution of compound 4 (1.0 equiv.), cyclohexylamine (1.2 equiv.) and base (1.2 equiv.) in solvent (0.2 M) was prepared and was flowed through the MACOS reactor using the specific reaction conditions detailed in the table. Isolated yield following silic gel chromatography using the flash technique

[b]Isolated yield after column chromatography