Published in final edited form as:

ACS Comb Sci. 2011 May 9; 13(3): 244–250. doi:10.1021/co100060x.

Automated Synthesis of a 184-Member Library of Thiadiazepan-1, 1-dioxide-4-ones

Erik Fenster^{†,§}, Toby R. Long^{†,‡,§}, Qin Zang[‡], David Hill[†], Benjamin Neuenswander[†], Gerald H. Lushington[†], Aihua Zhou[‡], Conrad Santini^{‡,†}, and Paul R. Hanson^{*,†,‡}

[†] Center for Chemical Methodologies and Library Development at the University of Kansas (KU-CMLD), 2034 Becker Drive, Delbert M. Shankel Structural Biology Center, Lawrence, Kansas 66047, United States

[‡] Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045, United States

Abstract

The construction of a 225-member ($3 \times 5 \times 15$) library of thiadiazepan-1,1-dioxide-4-ones was performed on a Chemspeed Accelerator (SLT-100) automated parallel synthesis platform, culminating in the successful preparation of 184/225 sultams. Three sultam core scaffolds were prepared based upon the utilization of an aza-Michael reaction on a multifunctional vinyl sulfonamide linchpin. The library exploits peripheral diversity in the form of a sequential, two-step [3 + 2] Huisgen cycloaddition/Pd-catalyzed Suzuki–Miyaura coupling sequence.

Keywords

thiadiazepan-1,1-dioxide-4-ones; parallel synthesis platform; aza-Michael reaction; Huisgen cycloaddition; Suzuki–Miyaura coupling

INTRODUCTION

Diversity-oriented synthesis (DOS) has emerged as a powerful strategy to produce large libraries of biologically relevant small-molecules for high throughput screening.^{1,2} Various strategies in this area hinge on the ability to generate diverse collections of molecules in the fewest number of steps possible.³ Among these, functional group pairing (FG-pairing) is a key concept that is at the heart of the “Build/Couple/Pair (BCP)” strategy pioneered by Schreiber and co-workers⁴ and continues to be the impetus for DOS-based library efforts. Previously, the inherent chemistry of vinyl sulfonamides was employed in a “Click, Click, Cyclize” strategy for the facile construction of skeletally diverse sultam scaffolds via

*Corresponding Author: phanson@ku.edu. Phone: (785) 864-3094. Fax: (785) 864-5396.

§Author Contributions

Equally contributing authors.

Supporting Information. Experimental procedures, tabulated results and data for this library, as well as full characterization for representative compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

synthetic operations on a single sulfonamide-based linchpin as outlined in Figure 1.⁵ In particular, thiadiazepan-1,1-dioxide-4-one scaffolds represent an under explored chemotype that was easy to access with the aforementioned strategy. We herein report the production of a 184-member library⁶ using an automated sequential alkyl azide cycloaddition/Suzuki-Miyaura coupling sequence on three core thiadiazepan-1,1-dioxide-4-one scaffolds which were constructed using an aza-Michael variant of the “Click, Click, Cyclize” method.

Sulfonamides have long been valued for their rich biological and chemical profiles rendering them a promising class of compounds in drug discovery.⁷ Cyclic sulfonamides (sultams), while not found in nature, exhibit a wide-array of potent biological activities⁸ that has inspired the present study aimed at mining underrepresented chemical space of the titled peptidomimetic chemotype⁹ in hopes of identifying new bioactive probes.

RESULTS AND DISCUSSION

Efforts toward the construction of the key thiadiazepan-1,1-dioxide-4-one scaffolds are outlined in Scheme 1. We envisioned utilizing two functional group handles in regions **A/B** on sultam scaffolds **5**{1–3} for the attachment of diverse appendages. The Huisgen [3 + 2] cycloaddition¹⁰ and Suzuki–Miyaura coupling reactions¹¹ were chosen based upon their well-precedented efficiency¹² and use in library development.¹³ The introduction of an alkyne group in quadrant **A** allows for facile diversification via the well-known Huisgen [3 + 2] cycloaddition, while installation of a bromophenyl group into quadrant **B** provides the necessary functionality for various Pd-catalyzed cross-couplings, such as the Suzuki–Miyaura reaction.

Each of the three sultam scaffolds **5**{1–3} were efficiently accessed using a FG-pairing strategy previously reported,^{3b,5c} in which L-alanine/valine/leucine methyl ester hydrochlorides underwent sulfonylation to generate vinyl sulfonamides **2**{1–3}. Subsequent alkylation of sulfonamides **2**{1–3}, followed by aza-Michael addition of propargyl amine, yielded the desired tertiary sulfonamides **4**{1–3}. Initially, the direct intermolecular lactamization from sulfonamides **4** was investigated as a one-step route to **5**. However, despite similar intramolecular transformations in the literature,^{9,14} little success was achieved. Efforts were next directed to a two-step hydrolysis/lactamization¹⁵ sequence to produce scaffolds **5**{1–3} in good overall yields on multigram scale.^{16,17}

With the desired scaffolds **5**{1–3} in hand, we next investigated the validation of the proposed library via diversification of regions **A** and **B**. The logical starting point relied on the noted selectivity and compatibility of the azide/alkyne [3 + 2] cycloaddition for its use in region **A**. In this regard, conditions employing Cu(I) catalysis (Table 1, entry 1) were initially explored and found to be high-yielding but unfortunately afforded an undesirable mixture of regioisomers. The use of Cu(II) catalysts in *t*-BuOH/H₂O, however, saw complete regioselectivity but suffered from poorer yields (Table 1, entry 2) attributed to poor substrate solubility. Additional optimization was achieved with the use of CH₂Cl₂ (Table 1, entry 3) or acetone (Table 1, entry 4) as cosolvents, which resulted in near quantitative yields. Use of lower catalyst/additive loadings was also explored to simplify library purification (Table 1, entries 4–6). Though catalyst loadings could be reduced to as low as 10 mol % without risking a substantial loss in yield, it was envisioned that an immobilized source of copper would be more amenable to parallel library synthesis. The use of copper immobilized on Amberlyst (A-21 · CuI)¹⁸ at 20 mol % in CH₂Cl₂, was found to afford the triazole-containing sultams **7**{1,2} in excellent yield (Table 1, entry 7).

We began investigations into the Suzuki–Miyaura coupling reaction using Pd(dppf)Cl₂ and Cs₂CO₃ in DMF/H₂O (Table 2, entries 1–4). Near quantitative yields could be achieved

with a catalyst loading of 5 mol % using relatively high temperatures and prolonged reaction times (Table 2, entry 4). However, these conditions resulted in difficult emulsions during the aqueous workups, a situation that renders the reaction impractical in a parallel platform. This problem was attributed to the choice of base/solvent combination utilized, and a number of alternative conditions were next explored (Table 2, entries 5–13). Ultimately, the combinations of Cs₂CO₃ in DME/H₂O provided the most convenient workup while retaining high yields (Table 2, entry 11).¹⁹

On the basis of the optimal conditions chosen for both reactions, studies turned toward combining the two reactions into a single-step sequence for ease of use in parallel synthesis (Scheme 2). Sultam **5**{1} was first reacted for 14 h with excess *p*-methoxybenzyl azide **6**{3} in the presence of A-21 · CuI, followed by filtration of the catalyst and concentration to yield crude, triazole-containing sultam **7**{1,3}.²⁰ Sultam **7**{1,3} was carried forward to the coupling event without further purification, upon which was sequentially added, DME, solid Pd(dppf)Cl₂, Cs₂CO₃ in H₂O, and excess boronic acid **8**{2} before heating at 85 °C for 14 h. After which time, a basic workup was performed to remove excess boronic acid and Cs₂CO₃ from the reaction mixture, followed by liquid–liquid extraction using CH₂Cl₂. The resulting solution was filtered via Si-SPE to remove residual Pd(0) and concentrated under reduced pressure to afford sultam **9**{1,3,2} in excellent yield over the combined two-step sequence. Overall, this sequence proved relevant in the transfer of chemistries to parallel methods in which both workup and purification were minimized.

The combined sequence was next attempted as a rehearsal 2 × 3 × 3 validation library using a Chemspeed Accelerator SLT-100 synthesizer²¹ (Table 3). Azides **6**{1–3} were chosen as diverse representative members of the final library. A small substrate scope for the Suzuki–Miyaura coupling reaction was also explored with the choice of electron-deficient and electron-rich phenyl, and alkyl boronic acids **8**. Using the two-step sequence described above in the Chemspeed platform (0.150 mmol scale), the resulting 18 crude sultams **9** were subjected to preparative HPLC purification. In general, yields in the range of 16–49% were obtained with purities >87%. However, boronic acid **8**{3} (cyclopropyl), was significantly less reactive and resulted in either no yield or low yields as compared to both phenyl boronic acids in the sequence (Table 3, entries 3, 6, 9, 12, 15, and 18). Overall, the results of the validation efforts demonstrated a successful two-step automated sequence.

With these results in hand, planning began for constructing the 225-member library using the Chemspeed platform with the conditions set in place during the rehearsal library. A number of azides and boronic acids were chosen (Scheme 3) based on differences in their structure and polarity. On the basis of the rehearsal library, alkyl boronic acids were excluded from the final library. Using the validated conditions, the Chemspeed was then programmed to run three consecutive 3 × 5 × 5 reactions (75 compounds each) for a total of 225 compounds.

Upon completion of the three 75-compound runs, a total of 225 reactions were purified via preparative/mass-directed HPLC in which 184 compounds were obtained with quantities ≥20 mg and with purity >90% starting from 0.150 mmol of sultams **5**{1–3}.²² Further analysis of the data revealed no definitive trends in yields between substrates and reagents; however it was evident that thiophene boronic acid (R³ = **5**) was the only reagent that yielded little or no material for the 15 reactions for which it was utilized.

In conclusion, we successfully completed the automated production of a 184/225-member library of thiadiazepan-1,1-dioxide-4-ones using a Chemspeed Accelerator platform in which a two-step diversification sequence was performed. The resulting compounds of this library are in the process of being distributed to a number of biological collaborators within

the NIH Molecular Libraries Probe Center Network (MLPCN) and future efforts will focus on the production of targeted libraries of thiadiazepan-1,1-dioxide 4-ones and related chemotypes, as well as their anticipated biological evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources

Financial support of this work was provided by the Institute of General Medical Sciences and is gratefully acknowledged (P50-GM069663 and P41-GM076302).

References

1. (a) Tan DS. Diversity-Oriented Synthesis: Exploring the Intersections Between Chemistry and Biology. *Nat Chem Biol.* 2005; 1:74–84. [PubMed: 16408003] (b) Thomas GL, Spandl RJ, Glansdorp FG, Welch M, Bender A, Cockfield J, Lindsay JA, Bryant C, Brown DFJ, Loiseleur O, Rudyk H, Ladlow M, Spring DR. Anti-MRSA Agent Discovery Using Diversity-Oriented Synthesis. *Angew Chem, Int Ed.* 2008; 47:2808–2812.
2. For reviews on DOS, see: (a) Tan DS. Diversity-Oriented Synthesis: Exploring the Intersections Between Chemistry and Biology. *Nat Chem Biol.* 2005; 1:74–84. [PubMed: 16408003] (b) Spandl RJ, Diaz-Gavilan M, O'Connell KMG, Thomas GL, Spring DR. Diversity-Oriented Synthesis. *Chem Rec.* 2008; 8:129–142. [PubMed: 18563806] (c) Schreiber SL. Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery. *Science.* 2000; 287:1964–1969. [PubMed: 10720315] (d) Arya P, Joseph R, Gan Z, Rakic B. Exploring New Chemical Space by Stereocontrolled Diversity-Oriented Synthesis. *Chem Biol.* 2005; 12:163–180. [PubMed: 15734644] (e) Shaw JT. Naturally Diverse: Highlights in Versatile Synthetic Methods Enabling Target-and Diversity-Oriented Synthesis. *Nat Prod Rep.* 2009; 26:11–26. [PubMed: 19374120] (f) Thomas GL, Wyatt EE, Spring DR. Enriching Chemical Space with Diversity-Oriented Synthesis. *Curr Opin Drug Discovery.* 2006; 9:700–712.
3. (a) Comer E, Rohan E, Deng L, Porco JA Jr. An Approach to Skeletal Diversity Using Functional Group Pairing of Multifunctional Scaffolds. *Org Lett.* 2007; 9:2123–2126. [PubMed: 17472394] (b) Zhou A, Rayabarapu D, Hanson PR. “Click, Click, Cyclize”: A DOS Approach to Sultams Utilizing Vinyl Sulfonamide Linchpins. *Org Lett.* 2009; 11:531–534. [PubMed: 19115841] (c) Wipf P, Stephenson CRJ, Walczak MAA. Diversity-Oriented Synthesis of Azaspirocycles. *Org Lett.* 2004; 6:3009–3012. [PubMed: 15330670] (d) Santra S, Andreana PR. A One-Pot, Microwave-Influenced Synthesis of Diverse Small Molecules by Multicomponent Reaction Cascades. *Org Lett.* 2007; 9:5035–5038. [PubMed: 17956113]
4. Nielsen TE, Schreiber SL. Organic Chemistry: Molecular Diversity by Design. *Angew Chem, Int Ed.* 2008; 47:48–56.
5. (a) Rolfe A, Lushington GH, Hanson PR. Reagent Based DOS: A Click, Click, Cyclize Strategy to Probe Chemical Space. *Org Biomol Chem.* 2010; 8:2198–2203. [PubMed: 20401396] (b) Zhou A, Rayabarapu D, Hanson PR. “Click, Click, Cyclize”: A DOS Approach to Sultams Utilizing Vinyl Sulfonamide Linchpins. *Org Lett.* 2009; 11:531–534. [PubMed: 19115841] (c) Zhou A, Hanson PR. Synthesis of Sultam Scaffolds via Intramolecular Oxa-Michael and Diastereoselective Baylis-Hillman Reactions. *Org Lett.* 2008; 10:2951–2954. [PubMed: 18553974] (d) Jiménez-Hopkins M, Hanson PR. An RCM Strategy to Stereodiverse δ -Sultam Scaffolds. *Org Lett.* 2008; 10:2223–2226. [PubMed: 18447383] (e) Rolfe A, Samarakoon TB, Hanson PR. Formal [4 + 3] Epoxide Cascade Reaction via a Complementary Ambiphilic Pairing Strategy. *Org Lett.* 2010; 12:1216–1219. [PubMed: 20178346] (f) Jeon KO, Rayabarapu D, Rolfe A, Volp K, Omar I, Hanson PR. Metathesis Cascade Strategies (ROM-RCM-CM): A DOS Approach to Skeletally Diverse Sultams. *Tetrahedron.* 2009; 65:4992–5000. [PubMed: 20161277]

6. 184 out of 225 members were successfully produced in sufficient quantities and purities (>10 mg and >90% purity).
7. (a) Drews J. A Historical Perspective. *Science*. 2000; 287:1960–1964. [PubMed: 10720314] (b) Navia MA. A Chicken in Every Pot, Thanks to Sulfonamide Drugs. *Science*. 2000; 288:2132–2133. [PubMed: 10896586]
8. For a comprehensive list of bioactive sultams, see ref ^{5d} and references cited therein.
9. de Bont DBA, Moree WJ, Liskamp RMJ. Molecular Diversity of Peptidomimetics: Approaches to the Solid-Phase Synthesis of Peptidosulfonamides. *Bioorg Med Chem*. 1996; 4:667–672. [PubMed: 8804531]
10. (a) Huisgen R, Knorr R, Moebius L, Szeimies G. 1,3-Dipolare Cycloadditionen, XXIII. Einige Beobachtungen zur Addition organischer Azide an CC-Dreifachbindungen. *Chem Ber*. 1965; 98:4014–4021. (b) Huisgen R, Szeimies G, Moebius L. 1,3-Dipolare Cycloadditionen, XXXII. Kinetik der Additionen organischer Azide an CC-Mehrfachbindungen. *Chem Ber*. 1967; 100:2494–2507. (c) Kolb HC, Finn MG, Sharpless KB. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew Chem, Int Ed*. 2001; 40:2004–2021.
11. Miyaura N, Yanagi T, Suzuki A. The Palladium-Catalyzed Cross-Coupling Reactions of Phenylboronic Acid with Haloarenes in the Presence of Bases. *Synth Commun*. 1981; 11:513–519.
12. (a) Miyaura N. Organoboron Compounds. *Top Curr Chem*. 2002; 219:11–59. (b) Kotha S, Lahiri K, Kashinath D. Recent Applications of the Suzuki-Miyaura Cross-Coupling Reaction in Organic Synthesis. *Tetrahedron*. 2002; 58:9633–9695. (c) Franzen R. The Suzuki, the Heck, and the Stille Reaction—Three Versatile Methods for the Introduction of New C–C Bonds on Solid Support. *Can J Chem*. 2000; 78:957–962. (d) Sasaki M, Fuwa H. Total Synthesis of Polycyclic Ether Natural Products Based on Suzuki–Miyaura Cross-Coupling. *Synlett*. 2004:1851–1874. (e) Stanforth SP. Catalytic Cross-Coupling Reactions in Biaryl Synthesis. *Tetrahedron*. 1998; 54:263–303.
13. (a) Cho CH, Neuenswander B, Larock RC. Diverse Methyl Sulfone-Containing Benzo[*b*]thiophene Library via Iodocyclization and Palladium-Catalyzed Coupling. *J Comb Chem*. 2010; 12:278–285. [PubMed: 20055500] (b) Zhou H, Zhang W, Yan B. Use Cyclohexylisocyanide and Methyl 2-Isocynoacetate as Convertible Isocyanides for Microwave-Assisted Fluorous Synthesis of 1,4-Benzodiazepine-2,5-Dione Library. *J Comb Chem*. 2010; 12:206–214. [PubMed: 19947585] (c) Jeges G, Nagy T, Meszaros T, Kovacs J, Dorman G, Kowalczyk A, Goodnow RA. Practical Synthesis of 5-Aryl-3-alkylsulfonyl-phenol and 5-Aryl-3-arylsulfonyl-phenol Libraries. *J Comb Chem*. 2009; 11:327–334. [PubMed: 19206513] (d) Agarkov A, Gilbertson SR. Preparation of a Library of Unsymmetrical Ureas Based on 8-Azabicyclo[3.2.1]Octane Scaffold. *J Comb Chem*. 2008; 10:655–657. [PubMed: 18611055] (e) Tan LP, Hao W, Yang PY, Kalesh KA, Zhang X, Hu M, Srinivasan R, Yao SQ. High-Throughput Discovery of Mycobacterium tuberculosis Protein Tyrosine Phosphatase B (MtpB) Inhibitors Using Click Chemistry. *Org Lett*. 2009; 11:5102–5105. [PubMed: 19852491] (f) Rogers SA, Melander C. Construction and Screening of a 2-Aminoimidazole Library Identifies a Small Molecule Capable of Inhibiting and Dispersing Bacterial Biofilms across Order, Class, and Phylum. *Angew Chem, Int Ed*. 2008; 47:5229–5231. (g) Pagliai F, Pirali T, Del Grosso E, Di Brisco R, Tron GC, Sorba G, Genazzani AA. Rapid Synthesis of Triazole-Modified Resveratrol Analogues via Click Chemistry. *J Med Chem*. 2006; 49:467–470. [PubMed: 16420033]
14. (a) Han C, Lee JP, Lobkovsky E, Porco JA Jr. Catalytic Ester-Amide Exchange Using Group(IV) Metal Alkoxide–Activator Complexes. *J Am Chem Soc*. 2005; 127:10039–10044. [PubMed: 16011366] (b) Robins MJ, Sarker S, Xie M, Zhang W, Peterson MA. Synthesis of 2',3'-Fused (3.3.0) γ -Butyrolactone-Nucleosides and Coupling with Amino-Nucleosides to Give Amide-Linked Nucleotide-Dimer Analogues. *Tetrahedron Lett*. 1996; 37:3921–3924. (c) Neogi S, Roy A, Naskar D. One-Pot Synthesis of New Fused 4,5-Bridged 1,2,5-Triazepine-3,6-diones, 1,2,5-Triazepine-3,7-diones Heterocycles by Petasis Reaction. *J Comb Chem*. 2010; 12:75–83. [PubMed: 19954206] (d) Durow AC, Long GC, O'Connell SJ, Willis CL. Total Synthesis of the Chlorinated Marine Natural Product Dysamide B. *Org Lett*. 2006; 8:5401–5404. [PubMed: 17078728]

15. Ho GJ, Emerson KM, Mathre DJ, Shuman RF, Grabowski EJJ. Carbodiimide-Mediated Amide Formation in a Two-Phase System. A High-Yield and Low-Racemization Procedure for Peptide Synthesis. *J Org Chem.* 1995; 60:3569–3570.
16. All three scaffolds were isolated as crystalline white foams with purity >95% as determined by ¹H NMR.
17. Partial racemization of **5**{1–3} was observed during the hydrolysis/lactamization sequence. For example, *ee* measurements of **5**{2} was found to be 38% when compared against a synthesized racemic sample. Further studies are focused on circumventing this issue.
18. Girard C, Onen E, Aufort M, Beauviere S, Samson E, Herscovici J. Reusable Polymer-Supported Catalyst for the [3 + 2] Huisgen Cycloaddition in Automation Protocols. *Org Lett.* 2006; 8:1689–1692. [PubMed: 16597142]
19. We also briefly explored the use of Pd-bound FibreCat whereby reaction workup consisted of a simple SPE filtration event, see: Colacot TJ, Carole WA, Neide BA, Harad N. Tunable Palladium-FibreCats for Aryl Chloride Suzuki Coupling with Minimal Metal Leaching. *Organometallics.* 2008; 27:5605–5611. Unfortunately, the fibrous nature of this reagent and its delivery and separation via automation proved difficult.
20. Note: Excess volatile azide/CH₂Cl₂ was removed during the process of concentrating the reaction mixture under reduced pressure.
21. Chemspeed Technologies. [accessed April, 10, 2010]. Home Page. <http://www.chemspeed.com/>
22. The standards for compound purity and quantity are based upon those requested for the National Institutes of Health's Molecular Libraries Small Molecule Repository (http://mlsmr.glp.gov/MLSMR_HomePage/submitcompounds.html). The compound purities were determined by reverse-phase HPLC with peak area (UV) at 214 nm.

Figure 1.
Use of a versatile vinyl sulfonamide linchpin to access skeletally diverse sultams.

Figure 2.

Crude purity, final purity, and yield from HPLC analysis of Chemspeed rehearsal $2 \times 3 \times 3$ library of thiadiazepan-1,1-dioxide-4-ones.

Scheme 1.
 Synthesis of Substituted Thiadiazepan-1,1-dioxide-4-one Scaffolds $\text{5}\{1-3\}$

Scheme 2.
 Combined Two-Step Diversification Sequence

Scheme 3.

Building Blocks for the $3 \times 5 \times 15$ Library of Thiadiazepan-1,1-dioxide-4-ones

Table 1

Validation of Huisgen [3 + 2] Cycloaddition

entry	catalyst	loading (mol %)	additive	equiv	solvent	yield (%)
1	CuI	10	2,6-lutidine	1.2	CHCl ₃	88 ^a
2	CuSO ₄ · 6H ₂ O	10	Na ascorbate	0.1	<i>t</i> -BuOH/H ₂ O 1:2	45
3	CuSO ₄ · 6H ₂ O	20	Na ascorbate	0.3	<i>t</i> -BuOH/H ₂ O/CH ₂ Cl ₂ 1:1:1	97
4	CuSO ₄ · 6H ₂ O	20	Na ascorbate	0.3	<i>t</i> -BuOH/H ₂ O/acetone 3:4:1	96
5	CuSO ₄ · 6H ₂ O	10	Na ascorbate	0.2	<i>t</i> -BuOH/H ₂ O/acetone 3:4:1	95
6	CuSO ₄ · 6H ₂ O	5	Na ascorbate	0.1	<i>t</i> -BuOH/H ₂ O/acetone 3:4:1	78
7	A-21 · CuI	20	none		CH ₂ Cl ₂	90

^aResulted in a mixture of 1,4- and 1,5-regioisomers in 4:1 ratio.

Table 2

Validation of the Suzuki–Miyaura Coupling Reaction

entry	R ²	R ³	catalyst	loading (mol %)	base	solvent	temp (°C)	time (h)	yield (%)
1	<i>p</i> -Me-Bn	phenyl	Pd(dppf)Cl ₂	1	Cs ₂ CO ₃	DMF/H ₂ O	70	8	46
2	<i>p</i> -Me-Bn	phenyl	Pd(dppf)Cl ₂	5	Cs ₂ CO ₃	DMF/H ₂ O	70	8	51
3	<i>p</i> -Me-Bn	phenyl	Pd(dppf)Cl ₂	10	Cs ₂ CO ₃	DMF/H ₂ O	70	8	68
4	<i>p</i> -Me-Bn	phenyl	Pd(dppf)Cl ₂	5	Cs ₂ CO ₃	DMF/H ₂ O	85	24	98
5	<i>p</i> -MeO-Bn	<i>p</i> -tolyl	Pd(dppf)Cl ₂	10	Cs ₂ CO ₃	DMF/H ₂ O	70	14	85
6	<i>p</i> -MeO-Bn	<i>p</i> -tolyl	Pd(dppf)Cl ₂	10	Na ₂ CO ₃	DMF/H ₂ O	70	14	10
7	<i>p</i> -MeO-Bn	<i>p</i> -tolyl	Pd(dppf)Cl ₂	10	K ₃ PO ₄	DMF/H ₂ O	85	16	92
8	<i>p</i> -MeO-Bn	<i>p</i> -tolyl	Pd(dppf)Cl ₂	10	K ₃ PO ₄	dioxane/H ₂ O	90	16	90
9	<i>p</i> -MeO-Bn	<i>p</i> -tolyl	Pd(dppf)Cl ₂	10	Cs ₂ CO ₃	dioxane/H ₂ O	75	14	62
10	<i>p</i> -MeO-Bn	<i>p</i> -tolyl	Pd(dppf)Cl ₂	10	Cs ₂ CO ₃	dioxane/H ₂ O	90	16	94
11	<i>p</i> -MeO-Bn	<i>p</i> -tolyl	Pd(dppf)Cl ₂	10	Cs ₂ CO ₃	DME/H ₂ O	85	16	89
12	<i>p</i> -MeO-Bn	<i>p</i> -tolyl	Pd(PPh ₃) ₄	10	Cs ₂ CO ₃	DME/H ₂ O	70	14	<5
13	<i>p</i> -MeO-Bn	<i>p</i> -tolyl	Pd(PPh ₃) ₄	10	CsF	DME/H ₂ O	80	14	61

Table 3

Chemspeed Rehearsal 2 × 3 × 3 Library of Thiadiazepan-1,1-dioxide-4-ones

entry	sulfam	azide	boronic acid	product	yield (%) ^a	purity (%) ^b
1	5{1}	6{1}	8{2}	9{1,1,2}	40	100
2	5{1}	6{1}	8{16}	9{1,1,16}	44	91
3	5{1}	6{1}	8{17}	9{1,1,17}	0	0
4	5{1}	6{2}	8{2}	9{1,2,2}	35	98
5	5{1}	6{2}	8{16}	9{1,2,16}	37	100
6	5{1}	6{2}	8{17}	9{1,2,17}	0	0
7	5{1}	6{3}	8{2}	9{1,3,2}	38	100
8	5{1}	6{3}	8{16}	9{1,3,16}	33	87
9	5{1}	6{3}	8{17}	9{1,3,17}	41	10
10	6{1}	6{1}	8{2}	9{2,1,2}	45	100
11	6{1}	6{1}	8{16}	9{2,1,16}	44	100
12	6{1}	6{1}	8{17}	9{2,1,17}	0	0
13	6{1}	6{2}	8{2}	9{2,2,2}	49	100
14	6{1}	6{2}	8{16}	9{2,2,16}	43	100
15	6{1}	6{2}	8{17}	9{2,2,17}	0	0
16	6{1}	6{3}	8{2}	9{2,3,2}	38	100
17	6{1}	6{3}	8{16}	9{2,3,16}	23	100
18	6{1}	6{3}	8{17}	9{2,3,17}	16	94

^a Purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy).
^b Purity was determined by HPLC with peak area (UV) at 214 nm.